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Clinical presentations and outcomes of necrotizing fasciitis in males and females over a 13-year period

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HIGHLIGHTS

- Majority of Necrotizing Fasciitis (NF) patients are males (74%).
- NF of abdomen and groin is significantly higher in females.
- Male patients are more severely ill with significantly more organ dysfunction.
- Hospital stay and mortality of NF in both genders are comparable.
- NF remains a challenging clinical problem in Qatar with a mortality rate ranging from 25 to 27% for both genders.

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ABSTRACT

Background: Necrotizing fasciitis (NF) is a rapidly progressive infection of fascia and subcutaneous tissue resulting in serious outcomes. We aimed to evaluate the clinical presentations, hospital course and outcomes of NF based on patient gender.

Patients and methods: All patients admitted with NF were enrolled in the study over a 13-year period in the main tertiary hospital in Qatar. Clinical presentations, co-morbidities, severity and outcomes were analyzed and compared in male and female patients.

Results: A total of 331 NF patients were identified with a mean age of 51 ± 15 years and male to female ratio of 3:1. However, Arab Qatari females were more frequently affected by NF in comparison to their male counterparts and south Asian females ($p < 0.001$), respectively. Female patients were older and had significantly higher incidence of abdominal and groin NF ($p < 0.004$). There were 13 cases with recurrent NF; 85% of them were males. Male NF patients had significantly higher rate of organ failure ($p = 0.02$), but there was no significant difference in the hospital length of stay as well as mortality in both genders. Overall, there were 85 (25.7%) deaths (23 females and 62 males).

Conclusion: Necrotizing fasciitis remains a life threatening entity. Although, NF is more common in males, Qatari females are more likely to develop NF than males. NF of abdominal wall and groin is significantly higher in females. Development of organ failure is more common in males with NF. NF remains a challenging clinical problem in Qatar with a mortality rate ranging from 25 to 27% for both genders.

1. Introduction

Necrotizing fasciitis (NF) is a rare medical and surgical emergency. It is an acute rapidly progressing necrotizing infection of fascia, subcutaneous tissue and skin accompanied by severe

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systemic toxicity and multiorgan dysfunction [1]. NF is a known clinical entity from the days of Hippocrates, but its awareness and reporting increased across the last three decade [2]. Various terminologies are used to describe NF such as hemolytic streptococcal gangrene, meleney ulcer, acute dermal gangrene, suppurative fasciitis, synergistic necrotizing cellulitis and necrotizing erypilias [3]. NF is a rare clinical entity in which infection spreads rapidly through the fascial plane causing severe systemic toxicity and involvement of multiple body organs, hence it is termed as limb and life threatening emergency [1,3]. Epidemiologic studies suggest that patients with advanced age are at greater risk for NF and one out of five patients may die [4]. However, early diagnosis and timely management may contribute to the improved survival. Early diagnosis of NF remains a challenge in its initial stages, as the clinical presentations are usually vague or non-specific and the overlying skin is relatively normal in appearance with no clear boundaries or palpable limitation between viable and non-viable tissues [5]. Patients' history, understanding of systemic toxicity and multi-organ dysfunction are essential for proper management of these patients [1,5]. There is a paucity of information on the occurrence and outcomes of NF based on the gender of patients. The aim of this study is to evaluate the clinical presentations, hospital course and outcomes of NF based on the patient gender in one of the rapidly growing economies in the Middle East, the state of Qatar.

2. Patients and methods

This study was approved by the Ethics Committee, at Medical Research Center, Hamad Medical Corporation (HMC), Qatar with IRB#14066/14. HMC is the only tertiary health care facility in Qatar. In January 2013, the country's population was 1,903,447; of which 1,405,164 were males and 498,283 females (2.8:1) [6]. However, the influx of male laborers (80% of population in Qatar are expatriates with a South Asian predominance) has skewed the gender balance and women represents just one-quarter of the population [7]. All patients admitted from January 2000 to December 2013 with operative notes clearly indicates the presence of the necrosis of fascia and subcutaneous tissues, or operative notes specifically mentioned the NF, or tissue histopathology confirmed the diagnosis of NF were included in this study.

Patients' demographics, co-morbidities, initiating factors, presenting signs and symptoms, initial blood work-up (including serum procalcitonin levels), number of debridements, severity of disease, affected body region, intensive care and hospital stay, recurrence of NF and outcomes of these patients were recorded. All parameters were compared according to the gender of the patients.

2.1. Definitions

SOFA (Sequential Organ Failure Assessment) score was calculated using parameters such as the ratio of partial pressure arterial oxygen and fraction of inspired oxygen ($PaO_2/FiO2$), platelets count, bilirubin level, Glasgow coma score, Mean Arterial Pressure (MAP), use of vasopressors, creatinine level and urine output [8]. The Laboratory Risk Indicator for Necrotizing Fasciitis (***LRINEC***) score was calculated using parameters such as CRP, WBC, hemoglobin, sodium level, creatinine concentration and glucose level [9].

2.2. Statistical analysis

Data were presented as proportions, median (range) or mean (±standard deviation), as appropriate. Baseline demographic characteristics, medical history, clinical presentation, and outcomes were compared between males and females. Analyses were conducted using Student–t test for continuous variables and Pearson chi-square (χ^2) or Fisher exact (if cell contain value less than 5) test for categorical variables. A 2-tailed $p < 0.05$ was considered significant. Data analysis was carried out using the Statistical Package for Social Sciences version 18 (SPSS Inc, Chicago, Illinois).

3. Results

During the study period, a total of 331 NF patients were identified with a mean age of 51 ± 15 years and male to female ratio of 3:1. NF was more likely to occur in males (74.3%). Overall, females affected with NF were 3 years older compared to the males (53.5 ± 16.3 vs. 50 ± 15; $p < 0.06$). Arab Qatari females were more frequently affected by NF than their male counterparts (76.5% vs. 48%, $p < 0.001$). On the other side, the proportion of affected non-Arab males was greater than their female counterparts (52% vs. 23.5%, $p < 0.001$). The majority of NF patients (n = 237; 78%) presented with local swelling. Pain disproportionate to the local swelling was observed in 208 (68.4%), and fever was present in 203 (66.8%) patients. The median duration of symptoms was 4 days (Table 1). There was no significant difference in the other presenting symptoms and number of debridement in both genders. Forty-three (13%) patients had history of trauma. Five (1.5%) patients had history of receiving intramuscular injections. However, the majority of patients (85.5%) were not having any history or event leading to occurrence of NF. The most common co-morbidities were diabetes mellitus (51.7%), hypertension (35.6%) and kidney disease (15%). With respect to the association of co-morbid conditions and NF, females had significantly higher incidence of coronary artery disease (22% vs. 12%, $P < 0.002$). Most frequently involved site of NF was lower limb (n = 175; 52.9%), followed by perineum and genitalia (n = 113; 33.7%). The site of infection also varied according to gender. Males had significantly higher perineum and genitalia associated NF (40.1% vs.15.2%, $P < 0.002$) whereas, females had significantly greater incidence of abdominal wall and groin NF (20% vs.8.5%, $P < 0.004$). The most frequent type of causative bacteria was Type II (monobacterial, 57.2%) followed by Type I (polybacterial, 31.9%) and Type IV (fungal, 10.9%). Based on the types of the causative bacteria (type I– IV), there were no statistical differences between males and females.

Table 2 represents the Laboratory findings along with the standard reference ranges. Most of the patients with NF had low serum sodium (133 ± 5.6 mmol/L) and hyperglycemia (serum glucose 12.5 ± 10.3 mmol/L). The median serum procalcitonin level was 10.5 (1–303) ng/ml. However, these laboratory results were comparable among both the genders.

Table 3 demonstrates the involvement of various microorganisms in NF. The most commonly isolated bacteria in NF patients were streptococcus (38.4%), followed by staphylococcus (36.6%) and bacteroides (21.5%).

Table 4 shows comparison of disease severity, ICU and hospital length of stay and outcomes based on the patient's gender. The median SOFA score was 9 (2–21), and the laboratory risk indicator for necrotizing fasciitis (LRINEC) score was 5 (1–9). Recurrent NF occurred in 13 patients (11 males and 2 females). Seventy-six (27.8%) patients had septic shock during the hospital course. The median duration of intensive care unit (ICU) and hospital stay were 5.5 (1–75) and 16 (2–295) days, respectively. Although, the laboratory findings were comparable among males and females, male patients with NF had higher disease severity and had significantly higher median SOFA score [10(2–21) vs. 8(6–19), $P < 0.02$] as compared to female patients. There were no significant differences in the development of septic shock, the ICU and total hospital length of stay in both sexes. In our study population, 85 patients died with an overall mortality rate of 25.7%. Although, the number of deaths was higher in males (62 vs. 23 females), the mortality

Table 1
Comparison of patients demography, clinical presentations and site of necrotizing fasciitis by gender.

	Overall	Female (n = 85)	Male (n = 246)	p-value
Demography				
Patients, n (%)	331	85 (25.7%)	246 (74.3%)	
Age (mean;year)	50.8 ± 15.4	53.5 ± 16.3	50 ± 15	0.06
Arabs	183 (55.3%)	76.5	48	0.001 for all
South Asian	148 (44.7%)	23.5	52	
Causes				
Trivial trauma	43 (13.0%)	10.1	17.3	0.15
Intramuscular injection	5 (1.5%)	0.0	2.4	0.19
No history of injury	283 (85.5%)	90.6	83.7	0.12
Clinical presentation (%)				
Swelling	237 (78%)	80	77	0.65
Pain	208 (68.4%)	72	67	0.4
Fever	203 (66.8%)	65	68	0.62
Duration of symptoms (days, median)	4 (1–30)	4 (1–30)	4 (1–30)	0.8
Number of debridements (median; range)	2 (1–8)	2 (1–7)	2 (1–8)	0.40
Comorbidities				
Diabetes Mellitus	167 (51.7%)	57	50	0.23
Coronary Artery Disease	46 (14.2%)	22	12	0.02
Chronic Kidney Disease	49 (15.2%)	14.6	15.4	0.87
Hypertension	115 (35.6%)	37.8	34.9	0.63
Chronic liver Disease	21 (6.5%)	3.7	7.5	0.22
Obesity	15 (6%)	8.2	3.3	0.05
Smoking	8 (2.4%)	0.0	3.3	0.09
Bedridden	28 (8.5%)	12.9	6.9	0.08
Traumatic paraplegia	3 (0.9%)	0.0	0.2	0.30
Site of infection (%)				
Lower limb	175 (52.9%)	51	54	0.62
Perineum & genitalia	113 (33.7%)	15.2	40.1	0.002
Abdomen & groin	38 (11.5%)	20	8.5	0.004
Chest & breast	8 (2.4%)	3.5	2	0.43
Face & neck	21 (6.3%)	8.5	7	0.24
Causative bacteria %				0.59 for all
Type I (Polybacterial)	88 (31.9%)	28.4	33.2	
Type II (Monobacterial)	158 (57.2%)	58.1	56.9	
Type III (Marine bacteria)	0	0	0	
Type IV (fungal)*	30 (10.9%)	13.5	9.9	

*Overlap with other bacteria could be there.

Table 2
Laboratory findings by gender among patients with necrotizing fasciitis.

	Overall (n = 331)	Females (n = 85)	Males (n = 246)	P-value
WBC (White blood cells) ($\times 10^3/\mu l$) (4–10)*	16.2 ± 8.6	15 ± 8.7	16.5 ± 8.4	0.2
Hb (Hemoglobin) (g/dl) (13–17)*	12.1 ± 9.8	11.4 ± 10.8	12.4 ± 9.5	0.45
PLT (Platelets) (10^9/l) (150–400)*	269 ± 201	277 ± 148	266 ± 217	0.67
Sodium (mEq/l) (135–145)*	133.5 ± 5.6	133 ± 6	134 ± 5	0.47
Glucose (mmol/l) (3.3–5.5)*	12.5 ± 10.3	13.6 ± 8.7	12.1 ± 10.8	0.26
Creatinine (μmol/l) (62–124)*	97 (26–1263)	87 (26–899)	102 (26–1263)	0.09
Procalcitonin (ng/ml) <0.5 low risk of sepsis* >2.2 high risk of sepsis	10.5 (1–303)	3.4 (1–182)	4.6 (1–303)	0.96

*Reference range.

difference was not statistically significant between males and females (p = 0.73) (Table 4).

4. Discussion

To date several studies have assessed epidemiology, management and outcomes of NF. The primary focus of our study is to explore the clinical presentation and outcomes based on gender distribution. The major strength of our study is the clinically relevance and impact of gender on NF which has not been investigated as a primary objective in prior studies. Table 5 shows the geographic distribution and association of gender with NF [4,5,10–16]. These studies showed male predominance irrespective of population distribution, worldwide. The present study showed that the proportion of male patients with NF predominated over females in a ratio of 3 to 1 which is close to the gender distribution in the Qatari community and is in consistence with the international figures (2–3:1) [17]. Although, the underlying gender

Table 3
Recipient and donor characteristics.

Micro-organisms, n (%)	
- Streptococcus	114 (38.4%)
- Staphylococcus	109 (36.6%)
- *E. coli*	34 (11.4%)
- Pseudomonas	23 (7.7%)
- Bacteroides	61 (21.5%)
- Klebsiella	23 (7.7%)
- Aeromonas	4 (1.3%)
- Enterococcus	14 (4.7%)
- Clostridium	3 (1%)
- Proteus	5 (1.7%)
- Morganella	2 (0.7%)
- Prevotella	6 (2%)
- Fungal	30 (10.9%)
- Monobacterial	158 (57.2%)
- Polybacterial	88 (31.9%)
Culture results, n (%)	
- Wound culture positive	227 (69%)
- Blood culture positive	65 (20%)
- Gram positive	206 (69%)
- Gram negative	92 (31%)

distribution in our analysis is the true representation of the population structure of Qatar. Predominance of male gender is mainly attributed to the rising demand of labor-intensive job in this rapidly developing country which could have some potential to skew the gender balance.

In our study, Arab Qatari females were more frequently affected by NF in comparison to their male counterparts and south Asian females ($p < 0.001$). Also, Qatari females were relatively older than males. South Asian males are more liable to NF in comparison to their female counterparts and this could be in part related to their occupations and associated comorbidities. For instance, South Asian males in Qatar are mainly involved in the manual or outdoor jobs, which increased risk for injuries (even trivial trauma) and exposure to humidity (poor humidity increases distribution and proliferation of microorganisms) [18].

The other findings include the significant association of NF of abdominal wall and groin with female gender. The most frequently isolated bacteria in our study population were streptococcus and staphylococcus. All the types of NF based on the causative bacteria were comparable in the 2 genders; however, Type I (polybacterial) was more prevalent among males in contrast to the other 3 types. Our patients most frequently presented with local swelling than pain and fever. Singh et al. [10] reported that 91% of their patients presented with local pain and tenderness. Earlier studies from USA showed that the swelling and redness of the affected area were the common presenting feature in NF patients [16,19]. Recently, Goh et al. reported that swelling of the affected area and pain were the common presenting symptoms [20]. The present analysis did not show gender tendency for clinical presentations although pain and swelling were more evident in females ($p = NS$). There was no significant difference initial blood work-up, duration of symptoms of NF in both genders. A previous study suggested that most of the NF patients may not have any precipitating factor on initial presentation [11]. Similarly, the majority of patients in the present report did not have a history or an event that could lead easily to the early diagnosis of NF.

There was no significant difference between the 2 genders in terms of comorbid conditions except for the incidence of coronary artery disease (CAD). CAD was significantly higher in female NF patients. It is well-known that the NF of perineum and genitalia is more common in males. Our study reconfirms this, but our findings showed that NF of abdominal wall and groin was significantly higher in female patients [21]. The present study suggests that the median SOFA score was significantly higher in male patients as compared to females ($P < 0.02$). Male and female groups were comparable for the LRINEC scores and number of debridements.

NF can be complicated with systemic toxicity and multiorgan dysfunction. Bacteria get seeded into the fascia and releases toxins, which cause fascial necrosis and produce a favorable atmosphere for bacterial growth with rapid spread of infection through the fascial planes [1,22,23]. In this study, patients with NF have at least two organs dysfunction (average SOFA score of 9). Multiorgan failure rate was more common in males.

Male patients had higher organ dysfunction and more severe disease however; there was no significant difference in the ICU stay, and total hospital stay by gender. In our series; aggressive surgical

Table 4
Severity & outcomes of necrotizing fasciitis by gender.

	Overall (n = 331)	Females (n = 85)	Males (n = 246)	p-value
SOFA score	9 (2–21)	8 (6–19)	10 (2–21)	0.02
LRINEC ≥ 6	161 (54.8%)	54	56	0.82
NF Recurrence	13 (3.9%)	2.5%	4.5%	0.19
ICU Stay (days)	5.5 (1–75)	5 (2–73)	6 (1–75)	0.2
Hospital stay (days)	16 (2–295)	17 (2–115)	16 (2–295)	0.72
Septic shock	76 (27.8%)	27.9%	27.8%	0.55
Mortality	85 (25.7%)	27% (n = 23)	25% (n = 62)	0.73

Table 5
Review of gender distribution and outcome from different nationalities.

Author	Origin	Duration (years)	Total cases	Male:female ratio	Mortality
Huang et al., 2011 [12]	Taiwan	7	472	2:1	12.1%
Wang et al., 2014 [4]	Taiwan	8	91	2.8:1	20.9%
Singh et al., 2002 [10]	India	–	75	2.6:1	27%
Taviloglu et al., 2005 [11]	Turkey	16	98	1.8:1	35%
Martinschek et al., 2012 [13]	Germany	30	55	1.6:1	16.4%
Afifi et al., 2008 [14]	Egypt	13	37	2.7:1	43%
Frazee et al., 2008 [15]	USA	12	122	1.8:1	16.4%
Dworkin et al., 2009 [16]	USA	4	80	1.6:1	15%
Surahio et al., 2009 [5]	Saudi Arabia	0.5	35	6:1	11.5%
Present study	Qatar	13	331	2.9:1	22%

debridements remain the treatment of choice for NF patients which was comparable among both genders. Recurrent NF is understudied in the literature, in our study there were 13 cases with recurrent NF; 85% of these patients were males. The few reported cases of recurrent NF were caused mainly by streptococcus or methicillin resistant staphylococcus aureus [24]. The mortality of NF in our cohort occurred in more than one fifth of cases and was consistent with the recently described mortality figures [4].

The overall mortality was high in the study population, and no gender preference was observed, however, it is of clinical importance and worth noting that the number of deaths was greater in males. Contrarily, Wang et al. recently revealed a significantly higher risk of death in female patients with NF [4].

The future practice for NF should focus on developing strategies for early diagnosis and management based on gender-specific risk factors, although the consideration of gender as a risk factor for NF still need further confirmation. Further research should emphasize on the development of gender-based prognostic tools considering the major risk factors, site of infection, clinical scoring system, complications and outcomes. So, there is a need of extensive research for assessing the magnitude of NF based on gender to modulate future aspects of treatment and clinical practice for NF patients.

4.1. Limitations

The retrospective design and relatively small sample size are limitations of the present study. Although 13 cases had repeated NF, the exact time for recurrence of NF was not specified in this analysis. Lack of CRP levels for comparison with procalcitonin is another limitation. Procalcitonin has been introduced recently in HGH so not all the NF in the past underwent procalcitonin assessed at admission. The present study shows that serum procalcitonin levels on admission could predict the development of septic shock in critically ill NF patients. However, the mortality was not predicted by the risk stratification that we followed in the study. Moreover, the surgical debridement performed was also not consistent with this reference range. The accurate information on post-discharge outcomes of NF is lacking which requires further prospective studies.

4.2. Conclusion

Necrotizing fasciitis remains a life-threatening entity with 26% mortality. Although NF is more common in males, Arab Qatari females were more frequently affected by NF in comparison to their male counterparts and south Asian females NF of abdominal wall and groin is significantly higher in females. Development of multiorgan failure is more common in males with NF. Male patients were more severely ill with significantly more organ dysfunction; however, there was no significant difference in length of stay in ICU or hospital. NF remains a challenging clinical problem in Qatar with a mortality rate ranging from 25 to 27% for both genders.

Ethical approval

This study was approved by the medical research center at HMC; IRB # 14066/14.

Sources of funding

No funding was received for this study.

Author contribution

NS: acquisition of data, writing manuscript and review of manuscript; AE: conception and design of the study, interpretation of data, writing manuscript and critical review of manuscript; INM; acquisition of data, writing manuscript and review of manuscript; AT: study design, acquisition of data, helped to draft manuscript and review of manuscript; HA: study design, acquisition of data and critical review of manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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