The Potential Prognostic Significance of the Laboratory Risk Indicator for the Necrotizing Fasciitis (LRINEC) Score in Necrotizing Fasciitis

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Rezumat

Semnificația potențială a prognosticului indicatorului de risc de laborator pentru fasceita necrozantă (LRINEC) în cazurile de fasceită necrozantă

Context: Discutăm despre rolul indicatorului de risc de laborator pentru fasceita necrozantă (LRINEC) asupra prognosticului acestei boli. Fasceita necrozantă (NF) se caracterizează prin răspândirea rapidă a infecției și a necrozei țesutului moale și a fasciei.

Metode: Treizeci de pacienți (17 bărbați, 13 femei, vârsta medie 57,5 ani) au fost tratați în perioada 2011-2016; au fost analizați retrospectiv în ceea ce privește vârsta, sexul, agenții microbiologici izolați, modalitățile de tratament și rata mortalității.

Rezultate: Majoritatea infecțiilor au fost detectate în perineu (14, 46,7%), alte localizări ale infecției fiind regiunea presacrală (3, 10%), regiunea abdominală după intervenție chirurgicală de elecție (10,33,3%) și intervenție chirurgicală de urgență (2, 6,7%). 53,3% dintre pacienți au prezentat cel puțin un factor comorbid predispozant, cum ar fi diabetul zaharat, hipertensiunea, cardiomiopatia și insuficiența cardiacă congestivă. Culturile de țesut au fost pozitive la 12 (40%) pacienți. Scorul mediu LRINEC la internare a fost de $8,5 \pm 2,85$. A existat o corelație puternică între scorul LRINEC și vârsta pacientului ($p = 0,018$, $R = 0,43$). Scorul LRINEC nu a fost afectat nici de sex, nici de prezența oricăror comorbidități. Pacienții au fost clasificați conform sistemului de stadializare Wang și Wong: 1 pacient în stadiul 1 (3,3%), 15 în stadiul 2 (50%) și 14 în stadiul 3 (46,7%); pacienții cu stadii Wang și Wong mai mari aveau scoruri LRINEC semnificativ mai ridicate. Rata mortalității este de 16,7%.

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Scorul mediu LRINEC al pacienților decedați a fost de $9,2 \pm 2,2$ și al pacienților în viață de $8,36 \pm 2,9$.

Concluzii: Chiar dacă scorul LRINEC și stadiul Wang și Wong au fost semnificativ legate de internarea la terapie intensivă, efectul lor direct asupra mortalității nu a fost semnificativ în studiul nostru.

Cuvinte cheie: fasceită necrozantă, indicator de risc de laborator pentru fasceita necrozantă, stadiile Wang și Wong, tratamentul fasceitei necrozante.

Abstract

Background: We discuss the role of Laboratory Risk Indicator for the Necrotizing Fasciitis (LRINEC) on the prognosis of this disease. Necrotizing Fasciitis (NF) is characterised by rapid spreading of infection and necrosis of the soft tissues and fascia.

Methods: Thirty patients (17 male, 13 female, mean age 57.5 years) were treated between 2011-2016 (in our center); they were analysed retrospectively regarding age, sex, isolated microbiological agents, modalities of treatment and mortality rate.

Results: The majority of the infections were detected in the perineum (14 patients). Other sites of infection were: the presacral region (3 patients), as well as abdominal region after elective (10 patients) and emergency surgery (2 patients), respectively. 53.3% of patients had at least one predisposing comorbid factor such as diabetes mellitus, hypertension, cardiomyopathy and congestive heart failure. The tissue cultures were positive in 12 patients. Mean LRINEC score on admission was 8.5 ± 2.85 . There was a strong correlation between LRINEC score and patient age ($p=0.018$, $R=0.43$). LRINEC score was affected by neither gender nor the presence of any comorbidities. The patients were classified according to Wang and Wong staging system, as follows: one patient in stage 1, 15 patients in stage 2 and 14 patients in stage 3. Patients with higher Wang and Wong stages had significantly higher LRINEC scores. The mortality rate was 16.7%. The mean LRINEC score of deceased patients compared to patients who were successfully treated was 9.2 ± 2.2 and 8.36 ± 2.9 .

Conclusion: Even though LRINEC score and Wang and Wong stage were significantly related with ICU stay, their direct effect on mortality wasn't significant in our study.

Key words: necrotizing fasciitis, laboratory risk indicator for necrotizing fasciitis, Wang and Wong stages, treatment of necrotizing fasciitis

Introduction

Necrotizing Fasciitis (NF) is a life threatening, polymicrobial necrotizing infection of subcutaneous soft tissues and fascial planes. Claude Colles (France) defined the necrotizing fasciitis in 1783, then Joseph Jones (USA) who reported the cases of gas gangrene treated in the American Civil War, made the first description of NF. In 1883 JA Fournier described this entity as a localised perineal soft tissue infection. Since its first description, the mortality rate has not changed and

remains to be reported between 25-35% (1,2). Difficulty of recognition and delay in the aggressive surgical debridement are the main causes for the high mortality rates (3). Diabetes mellitus (DM), malnutrition and immunosuppression are well-known predisposing factors for developing NF (3).

Early diagnosis, appropriate antimicrobial therapy and aggressive debridement are key factors of successful NF treatment (4). As distinguishing NF from other soft tissue infections in the early phase of its course, precise diagnosis and staging is important to

achieve good treatment results. Wang and Wong staging, first described in 2005 by Yi-Shi Wang and Chin-Ho Wong is a chronological categorization of the skin manifestations as the disease progresses through early to late stages (5). The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) is a six-parameter scoring system designed to differentiate NF from other soft tissue infections. LRINEC scores > 6 have a specificity higher than 90% and sensitivity higher than 95% for the diagnosis of NF (6). Beside being an useful diagnostic tool, the LRINEC score was also found to have some prognostic value in some studies. The aim of our study is to evaluate LRINEC score and Wang and Wong classification as a prognostic tool for the patients treated with NF.

Methods

After institutional review board approval, retrospective analyses were performed on medical reports of all patients treated with the diagnosis of NF in the University of Health Sciences, Gaziosmanpaşa Taksim Training and Research Hospital, Turkey between 2011 and 2016. Thirty three consecutive patients with the diagnosis of NF were identified from the hospital medical record data base. Diagnosis of necrotizing fasciitis was provided according to the operative findings such as greyish colour of the debrided necrotizing fascia, easy detachment of normally adherent fascial planes, lack of bleeding on the cut surface of the involved fascia and the presence of dish water pus odor. Histopathologic tissue confirmation of the diagnosis was performed if available.

Of the initial 33 patients, 30 patients who

Table 1. LRINEC Scoring system (a score ≤ 5 points indicate a low risk for NF; 6-7 points indicate an intermediate risk of NF; ≥ 8 points indicate a high risk of NF)

Variables	Score
C-reactive Protein(mg/L)	
< 150	0
≥ 150	4
Total white blood cell count (per mm ³)	
<15	0
15-25	1
>25	2
Hemoglobin (gr/dL)	
>13.5	0
11-13.5	1
<11	2
Sodium (mmol/L)	
≥ 135	0
<135	2
Creatinin(mg/dL)	
≤ 1.6	0
>1.6	2
Glucose (mg/dL)	
≤ 180	0
> 180	1

had fully available medical reports for LRINEC score and Wang and Wong Classification in the first admission day were included in the study. LRINEC Score was calculated by considering six biological variables: C-reactive protein (CRP), white blood cell count, hemoglobin, creatine, glucose and sodium levels (4,5)(Table 1). The Wang and Wong staging was applied according to the original description (Table 2).

Statistical Analysis

The statistical analysis was performed using the SPSS software version 20. The variables were assessed by means and standard

Table 2. Wang and Wong stage description

	Stage 1 (early)	Stage 2 (intermediate)	Stage 3 (late)
Clinical features	Tenderness to palpation (extending beyond the apparent area of skin involvement) Erythema Swelling Calor (warm skin)	Blister or bullae formation serous fluid)	Crepitus Skin anesthesia Skin necrosis with dusky discoloration

deviation, after checked for normality in a preliminary analysis (visual and analytical methods were used). For the variables with no normal distribution, median and range was reported. The variables were assessed by frequency. For normally distributed variables, independent-samples *t* test and Pearson correlation coefficient were used for statistical analysis. The Mann-Whitney U test was used when the groups were small and / or the data was non-normally distributed or qualitative. Logistic regression was used to determine independent predictive factors of patient outcome. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. For an easier interpretation of the multivariate analysis, the Relative Risk (RR) with 95% confidence interval were presented. A *p*-value of less than 0.05 was considered to show statistically significant result.

Results

Seventeen of 30 patients, were male and 13 were female. The median age was 57.5 (20-81) years. The majority of the infections were detected in the perineum, as a consequence of perianal abscess (14 patients). Other sites of infection were: the presacral region due to pilonidal cyst abscess (3 patients), abdominal

region after elective and emergency surgery (10 and 2 patients respectively) (Fig. 1). More than half of the patients (16) had at least one predisposing comorbid factor such as diabetes mellitus, hypertension, cardiomyopathy and congestive heart failure. The most frequent (50%) comorbid factor was diabetes mellitus.

The tissue cultures were positive in 12 patients, half of whom were type 1 (polymicrobial) and the other half were type 3 (monomicrobial gram negative bacteria). The most common isolated microbiological agents were *E. Colli*, *Acinetobacter* spp and *Pseudomonas aeruginosa*.

Mean LRINEC score on admission was 8.5 ± 2.85 . Five patients had LRINEC scores < 6 and 25 patients had scores of 6 or more. There was a strong correlation between LRINEC score and patient age ($p=0.018$, $R=0.43$). LRINEC score was affected by neither gender nor the presence of any comorbidities ($p=0.24$ and $p=0.10$ respectively). Although patients with higher LRINEC scores had longer hospital stay, the relation between LRINEC score and hospital stay was not significant (Table 3).

When the patients were classified according to the Wang and Wong staging system, there was one patient in stage 1, 15 in stage 2 and 14 in stage 3, respectively. When stage 1 and 2

Figure 1. Etiology of necrotizing fasciitis

Table 3. Relations between the possible factors that may affect the outcome of NF, LRINEC scores and Wang and Wong classification.

Factors	LRINEC		p-value	Wang & Wong stage		
	Score < 6 (N=5)	Score ≥ 6 (N=25)		Stage 1+2	Stage 3	p-value
Age (years)	29(20-50)	60(25-81)	0.001*	50.1±18	60.6±8.3	0.07
Gender						
Male	4	13	0.240**	10	7	0.49
Female	1	12		6	7	
Comorbidities						
Yes	1	15	0.10**	8	8	0.69
No	4	10		8	6	
Hospital stay (days)	14(9-24)	21(4-92)	0.210*	20.7±12.2	25.7±22	0.59

*Mann-Whitney test

** Chi-square Test

patients were classified together as “low stage” group and stage 3 patients as “high stage” group, no statistically significant differences between these two groups was noted in regards to age, gender and the presence of any comorbidities. Patients classified as stage 3 had longer hospital stay but the difference did not reach statistical significance, either (*Table 3*).

Patients with higher Wang and Wong stages had significantly higher LRINEC scores (*Table 3, 4*). Twelve (40%) patients needed Intensive Care Unit (ICU) stay during the course of their treatment. Patients requiring ICU stay had higher LRINEC scores at admission (*Table 4*), as well as significantly higher Wang and Wong

stage (*Table 5*).

The mortality rate is 16.7%. The mean LRINEC score of deceased patients was 9.2±2.2 and 8.36±2.9 in patients who survived. Wang and Wong stage, LRINEC score and other possible factors that may be related with mortality such as age, gender and presence of any comorbidity were investigated. In univariate analyses, only older age was significantly related with mortality. In the multivariate analysis, age was once again detected as the only factor related to in patient mortality (RR=1.17, 95% CI:1.01-1.36, p=0.03) (*Table 6*). Even though the LRINEC score and Wang and Wong stage

Table 4. Relations between LRINEC scores and Wang and Wong stages, LRINEC scores and ICU stay

		Number of Patients	Mean LRINEC Score	p
Wang and Wong Stage	Low(Stage1+2)	16	7.5±3.09	0.037*
	High(Stage 3)	14	9.64±2.09	
ICU Stay	Yes	12	10.08±1.97	0.01*
	No	18	7.44±2.89	

*Independent sample t test

Table 5. ICU stay and Wang and Wong stages

	Low Wang and Wong Stage	High Wang and Wong Stage	p value
ICU stay			0.001*
Yes	2(12.5%)	10(71.4%)	
No	14(87.5%)	4(28.6%)	

*Chi square

Table 6. Univariate and Multivariate Analyses of In Hospital Mortality

Risk Factor for Mortality	Univariate Analyses				Multivariate Analyses*			
	RR	95% CI for RR		P value	RR	95% CI for RR		P value
		Lower	Upper			Lower	Upper	
Gender(female vs male)	0.44	0.06	3.15	0.41	0.40	0.03	5.36	0.49
Presence of a comorbid factor (No vs Yes)	1.38	0.19	9.76	0.74	0.46	0.28	7.51	0.58
LRINEC Score	1.12	0.77	1.62	0.54	0.95	0.47	1.91	0.90
Wang and Wong Stage (high vs low)	1.90	0.27	13.4	0.51	0.66	0.35	12.7	0.78
ICU Stay (no vs yes)	2.66	0.37	19.06	0.32	2.08	0.18	23.19	0.55
Age	1.17	1.01	1.36	0.03	1.17	1.01	1.36	0.03

*Logistic regression Backward LR

were significantly related with ICU stay, their direct effect on mortality wasn't significant in our study.

Discussion

In 1883, JA Fournier, a specialist in dermatovenerology, described localised necrotizing infection of the perineum in five male patients. Although large series report necrotizing fasciitis as being more common in males (3,7), a few studies reported that females were more commonly affected (8,9). In our study, despite the fact that males were predominantly affected, male/female ratio was relatively close (1:3). Our balanced gender distribution can be attributed to NF localisation in our patients. NF was located in anatomical regions other than the perineal area in more than half of our patients.

Patients with NF are usually in their fifties (2,7). In our study, median age was 57.5 years (20-81), which is consistent with previous studies. In some studies advanced age was considered as an independent predictor of mortality (10,11). McHenry et al showed that older patients had significantly higher mortality rates in their series (19). El-Menyar et al confirmed that finding in their larger series with 294 patients (12). Our findings were consistent with previous studies. In our study, all deceased patients were aged 60 years or older. In univariate analyses, older patients had significantly more mortality rates. In multivariate analyses, older age was determined as the only factor effecting mortality in our study.

NF can develop in any region of the body. Perineum is one of the most common sites for NF (12). In our study, consistent with literature, perineum was the most common localisation of NF; in cases of urogenital localisation there was no testicular involvement in our cases.

The dominant co-morbid diseases in NF are diabetes mellitus, obesity and hypertension (2,13). Diabetes mellitus was the most common co-morbid disease in our study.

The LRINEC score was first described in 2005 to distinguish NF from other soft tissue infections. A score 6 or more has 92% positive predictive value and 96% negative predictive value for the diagnosis of NF. It is useful to stratify patients as low (score 5 or less, probability of NF < 50%), medium (6-7, probability of NF c. 50-75%) and high risk (8 or more, probability of NF > 75%) risk of NF, in order to achieve a timely diagnosis and plan appropriate therapy (5). In a study by Colak et al (9) which investigated 25 patients with NF, mean LRINEC score was 4.6±2.7. Another large cohort by El-Menyar et al (12) with 294 NF patients, mean LRINEC score was 6.28±2.9 and 45% of patients had LRINEC score < 6. In our study only 5 patients (16%) were in low LRINEC group (Table 3) and our mean LRINEC score value was 8.5±2.8. Our high mean LRINEC score rates could be related to delay in diagnosis or delay in referral to the hospital.

Wang and Wong staging reflects chronological skin changes during the course of NF. Since underlying fascia is the source of infection in

NF, skin manifestations are secondary changes due to progressive ischemia. In stage 1 disease, skin manifestations like swelling and calor are indistinguishable from other soft tissue infections. In stage 2, due to progressive infection of deep fascia, perforator vessels supplying the skin become progressively thrombosed, which leads to consecutive blisters and bulla formation. In stage 3, progressive ischemia results in hemorrhagic bullae, skin anesthesia, and skin gangrene (5). In our study, there was a strong correlation between Wang and Wong stage and LRINEC score ($p=0.037$). Patients with high Wang and Wong stages tend to have high LRINEC scores (Table 4). To the best of our knowledge, this is the first description of the aforementioned correlation in the English Literature.

The mortality of NF is reported as approximately 25% (12). Although DM is a well known predisposing factor for NF, its effect on mortality is less clear. Yilmazlar et al could not detect DM as a prognostic factor in their study (15). In their 60 patients-series, Kalaivani et al did not show a correlation between mortality and DM (16). In our study, as with previous ones, neither DM nor other co-morbid factor was associated with mortality.

Gender could be another factor related to mortality. A study authored by Misiakos et al, showed that female gender was found to have significant association with mortality (17). In contrast with that study, Yanar didn't detect a relationship between gender and mortality in their series (18). Our study also did not detect a significant association between gender and mortality.

Besides its diagnostic use, LRINEC score was also determined as a predictor of mortality in some studies (9,19,20). In their study of 209 patients, Su et al reported that mortality in patients with LRINEC score ≥ 6 was significantly higher. They did not, however, detect a significant difference in hospital stay between patients with LRINEC score ≥ 6 or < 6 , respectively. In contrast, El-Manyar et al showed a significant difference in mortality between patients with LRINEC scores below or above 6. Also, there was a significant difference in

hospital stay between two groups in their study. On the other hand, Corona et al could not determine a significant difference in mortality between patients with LRINEC scores below and above 6, although non-surviving patients tended to have high scores (21). In our study, although non-surviving patients had higher LRINEC scores, there was no statistically significant difference in terms of mortality in patients depending on LRINEC score. Although patients with high LRINEC scores tend to have longer hospital stay, the relationship was not significant. ICU admission was significantly higher in patients with high LRINEC scores.

Wang and Wong staging is a clinical staging system of necrotizing fasciitis based on the evolving cutaneous features. Stage migration from early to late stage necrotizing fasciitis is evident in the majority of patients. In our study, we investigated the relationship between Wang-Wong stages and mortality. Stage 3 patients tended to have longer hospital stays. Even though there was not a significant relationship between mortality and Wang-Wong stages, we reported significantly higher rates of ICU admissions in patients stage 3 or higher. Also Wang-Wong stage 3 patients has significantly higher LRINEC scores.

Retrospective design and limited patient number were limitations of our study.

Conclusion

Results of our study LRINEC score and Wang & Wong staging are useful to detect necrotizing fasciitis severity. While all patients with higher LRINEC scores and who were classified as "high risk" in Wang & Wong classification had longer hospital stay, we could not notice a significant relationship with mortality rate.

Conflict of Interest

The authors declare no conflicts of interests.

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