



Original article

Usefulness of a risk scale based on procalcitonin for early discrimination between necrotizing fasciitis and cellulitis of the extremities[☆]



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ABSTRACT

Background and objective: To assess the usefulness of a risk scale based on serum procalcitonin (PCT) compared to the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scale in the early discrimination between necrotizing fasciitis (NF) and cellulitis of the extremities.

Materials and methods: Retrospective study of consecutive patients with confirmed diagnosis of NF in one limb ($n = 11$). This study group was compared with 23 consecutive patients with a diagnosis of severe limbs cellulitis during the same period. The clinical data and laboratory parameters were analyzed, the main variable was the serum level of PCT upon admission. The capacity for NF diagnosis of the two methods, PCT level and LRINEC scale score, were evaluated by ROC curve and determined by the calculation of the area under the curve (AUC).

Results: The AUC was significantly higher with PCT measurement, both as a continuous variable and when the risk was categorized. The cut-off point for the PCT level with the highest AUC under the curve was from 0.87 ng/ml (sensitivity 90.9%, specificity 82.6%), whereas it was a score of 5 on the LRINEC scale (sensitivity 72.7%, specificity 82.6%).

Conclusion: PCT measurement was a more effective method than the LRINEC score for early discrimination between NF and cellulitis of the extremities. A low level of PCT, associated with the patient's clinical status and physical examination is especially useful to rule out an early diagnosis of NF.

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Utilidad de una escala de riesgo basada en la procalcitonina sérica para la discriminación temprana entre fascitis necrosante y celulitis de las extremidades

RESUMEN

Fundamento y objetivo: Valorar la utilidad de una la escala de riesgo basada en la procalcitonina sérica (PCT) comparada con la escala *Laboratory Risk Indicator for Necrotizing Fasciitis* (LRINEC) en la discriminación precoz entre la fascitis necrosante (FN) y la celulitis en las extremidades.

Material y método: Estudio retrospectivo de pacientes consecutivos con diagnóstico confirmado de FN en una extremidad ($n = 11$). Ese grupo de estudio fue comparado con 23 pacientes consecutivos con

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diagnóstico de celulitis severa en miembros en el mismo periodo. Se analizaron los datos clínicos y los parámetros rutinarios de laboratorio, siendo la variable principal el nivel sérico de PCT al ingreso. La capacidad de discriminación para el diagnóstico de FN de los dos métodos —nivel de PCT y puntuación de la escala LRINEC— fue evaluada mediante la curva COR y determinada por el cálculo del área bajo la curva (ABC).

Resultados: El ABC fue significativamente mayor con la medición de la PCT, tanto como variable continua como cuando el riesgo era categorizado. El punto de corte para el nivel de PCT con mayor ABC bajo la curva fue a partir de 0,87 ng/ml (sensibilidad 90,9%; especificidad 82,6%), mientras que alcanzaba una puntuación de 5 en la escala LRINEC (sensibilidad 72,7%; especificidad 82,6%).

Conclusión: La medición de la PCT fue un método más efectivo que la escala LRINEC para discriminar precozmente entre FN y celulitis de las extremidades. Un nivel bajo de PCT, asociado al cuadro clínico y a la exploración física, es de especial utilidad para descartar el diagnóstico precoz de FN.

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Introduction

Necrotizing fasciitis (NF) is a serious infection that can lead to amputation and even death in case of delayed treatment,¹ which includes aggressive surgery and antibiotic therapy. However, an early diagnosis may be difficult to differentiate from other soft tissue infections with a better prognosis, such as limb cellulitis. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, based on six routine biochemical and hematological laboratory parameters, was suggested in 2004 by Wong et al.² for the early differential diagnosis of NF. In several studies, the LRINEC score has been reported to be quite effective.^{3,4} However, its usefulness has been questioned by other authors.^{5,6} Su et al.⁷ did not find LRINEC useful for the diagnosis of NF, but they did for its prognosis. Foo et al.⁸ reported a low level of diagnosis in immunosuppressed patients.

Serum procalcitonin (PCT) has been used as a reliable marker in the diagnosis, evolution and effectiveness of treatment in various serious bacterial infections and sepsis.⁹ Al-Thani et al.¹⁰ reported a positive correlation between LRINEC and PCT levels in predicting septic shock in patients with NF. However, these authors included patients with NF from various locations.

The aim of this study was to assess the usefulness of a PCT-based risk scale for early discrimination between NF and cellulitis of the limbs.

Material and methodology

A retrospective case-control study. From the database of our service, 11 consecutive patients were identified with the confirmed diagnosis of NF in a limb between 2009 and 2017. All these patients presented characteristic signs of NF during surgical debridement, such as devitalized fascia of easy digital dissection between planes, purulent exudate or in “dishwashing water”, absence of bleeding and regional vascular thrombosis. The diagnosis of NF was confirmed by histopathological study in all these patients.

For the control group, 55 patients were consecutively treated in the same period of time with the diagnosis of severe limb cellulitis. Criteria for severe non-necrotizing soft tissue infection were clinical signs, need for hospitalization for more than 48 h, the use of parenteral antibiotics for more than 48 h, presence of abscesses that required surgical debridement, the evolution of the process and negative biopsy. PCT was requested for 23 of these patients at the time of admission and they were used as controls for this study.

Assessment

The following data was gathered from the patients of both groups: gender, age, affected limb, comorbidities; parameters to calculate LRINEC (PCR, creatinine, hemoglobin, leukocyte count,

glucose, serum sodium) and PCT levels at admission. In addition, the evolution, the need for amputation and, where appropriate, mortality were also recorded.

According to the LRINEC² score, the risk of NF was classified as low if the index was below 6, moderate if it was 6–7 and high risk if it was above 7. Regarding PCT, the risk was classified¹⁰ as low when serum levels were below 0.5 ng/ml, moderate between 0.5 and 1.9 ng/ml and high with levels 2 ng/ml or higher.

Statistical analysis

All of the statistical analyses were performed using the SPSS v.22 software. The results were shown as median and interquartile range for quantitative variables, and as absolute frequency for qualitative variables. We used the non-parametric Mann–Whitney *U* test to compare between quantitative variables. To compare the qualitative variables, Fisher's exact test and likelihood ratio were used. The relationship between risk categories was assessed using Spearman's rank-order correlation. To determine the discrimination ability between NF and cellulitis by using LRINEC score and the serum PCT level, we created a receiver-operating characteristic curve (ROC). And using the area under the curve (AUC) and the Youden Index we determined the cut-off point with greater sensitivity and specificity with every method. For all analyzes we considered the statistical significance for values of $p < 0.05$.

Results

The characteristics of both groups are shown in Table 1. Regarding the admission parameters, there were significant differences in the average levels of hemoglobin ($p = 0.031$), LRINEC ($p = 0.005$) and PCT ($p < 0.001$), being significantly higher in the NF group. Comparing both risk indicators of NF, the moderate or higher risk was significantly higher in the NF group using either the LRINEC score ($p = 0.007$) or with the serum PCT level ($p = 0.002$). The risk indicated by LRINEC and PCT had a moderate direct correlation ($r = 0.52$; $p = 0.001$).

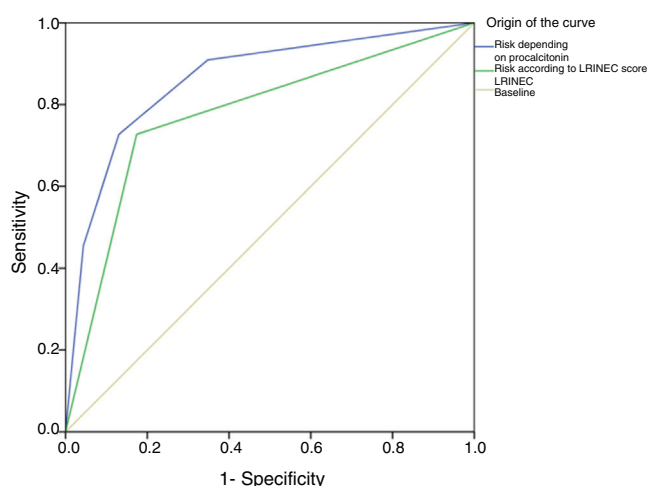
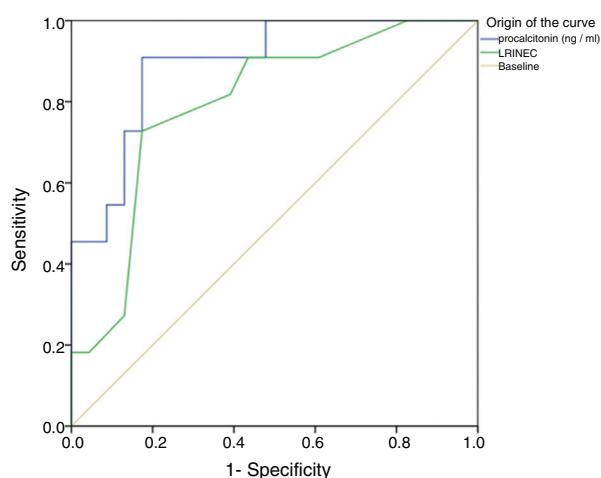
Through the ROC curve, the AUC was larger for the risk classified using the PCT method compared to the LRINEC score (Fig. 1). Likewise, when comparing the results from both methods as continuous variables, the PCT level also showed a larger AUC. The cut-off point with the largest area under the curve (Fig. 2) was a level >0.87 ng/ml with PCT (sensitivity 90.9%; specificity 82.6%), and >5 points in LRINEC (sensitivity 72.7%; specificity 82.6%).

There were 3 amputations and other 3 deaths, all in the NF group ($p = 0.028$). The group of NF patients had a longer hospitalization time, with a median of 24 days, compared to the 3 days of the cellulitis group ($p < 0.001$).

Table 1
Characteristics of both groups.

Variable	NF, n = 11	Cellulitis, n = 23	p
Sex (female/male)	6/5	9/14	0.475
Age (years)	51.7 (43) [23–84]	59.3 (29.7) [28–82]	0.326
Lower/upper limb	8/3	18/5	0.999
Diabetes mellitus (Yes/No)	3	7	0.999
HIV (Yes/No)	1	1	0.999
HCV (Yes/No)	2	1	0.239
CHF (Yes/No)	2	3	0.999
CKF (Yes/No)	2	1	0.239
Liver cirrhosis (Yes/No)	1	0	0.324
RA (Yes/No)	1	1	0.999
PCR (mg/l)	182 (178) [39–507]	122 (127.6) [8.7–315]	0.071
Creatinine (mg/dl)	1.27 (1.77) [0.4–7.8]	0.86 (0.19) [0.5–1.4]	0.123
Hemoglobin; g/dl	12.4 (3.2) [8.5–14.2]	13.8 (2.5) [7.3–15.1]	0.031**
Leucocytes ($\times 10^9/l$)	14 (6.9) [0.7–29.4]	11.9 (7.8) [2.9–22.7]	0.913
Blood glucose level (mg/dl)	123 (78) [80–276]	119 (49) [75–276]	0.800
Serum sodium (meq/l)	134 (10) [127–143]	138 (4) [130–145]	0.308
LRINEC	6 (3) [1–10]	2 (3) [0–8]	0.005**
LRINEC risk (low/moderate/high)	3/6/2	19/3/1	0.007**
Procalcitonin (ng/ml)	3.81 (57.6) [0.3–400]	0.22 (0.45) [0–10.9]	<0.001**
Procalcitonin risk (low/moderate/high)	1/2/8	15/5/3	0.002**

Continuous variables: median (interquartile range) [range].

** $p < 0.05$.**Fig. 1.** ROC on discrimination ability in the diagnosis of NF depending on the risk calculated by the level of procalcitonin (AUC: 0.86; CI 95%: 0.72–1) versus the LRINEC score (AUC: 0.77; CI 95%: 0.59–0.95) as categorical variables.**Fig. 2.** ROC on the ability to discriminate in the diagnosis of NF depending on the level of procalcitonin (AUC: 0.89; 95% CI: 0.78–1) versus the LRINEC score (AUC: 0.79; 95% CI: 0.63–0.95) as continuous variables.

Discussion

The LRINEC score is based on 6 laboratory parameters (Hb, leukocytes, glucose, sodium, creatinine and C-reactive protein), which with different weight provide a score between 0 and 13 points, and where a score of 6 or more points suggests a NF diagnosis and below that a cellulitis diagnosis.² A systematic review of the literature found the usefulness of the LRINEC score for early NF diagnosis. However, Su et al.⁷ were not able to find a relationship between LRINEC and the diagnosis of NF, although they did report its usefulness in its prognosis, where a score over 6 was related to higher mortality and number of amputations. Another study⁸ found a low predictive level of the LRINEC score in immunosuppressed patients. On the other hand, it is noteworthy that among the previous studies that only analyzed the NF of the limbs,^{11–31} the high values of the LRINEC score were only associated with a longer hospital stay.¹¹

This disparity in results has led to the analysis of other potential biomarkers for the early diagnosis of NF. PCT is a peptide precursor of the hormone calcitonin, which is involved in calcium homeostasis. The PCT level increases in response to a pro-inflammatory stimulus, especially of bacterial nature.¹² During a bacterial infection PCT is mainly produced by the cells of lungs and intestine, and is a reliable marker in the diagnosis and treatment of serious bacterial infections and sepsis.⁹

Although in previous studies the score defined was 6 or more points on the LRINEC score for the diagnosis of NF,^{2,3} patients with NF in this study had an average score of 6 points on the LRINEC score, ranging from 3 to 9. However, PCT serum levels over 0.87 ng/ml showed a significantly higher sensitivity. This discrepancy between the two methods on diagnostic effectiveness became clear when correlation between them was only moderate.

Studies on the use of PCT in patients with NF are rare in the literature. Al-Thani et al.¹⁰ analyzed the prediction of septic shock in patients with NF, establishing a cut-off point of 5.6 ng/ml. Friederichs et al.¹³ also analyzed the prognosis value of PCT in relation to treatment, noting that PCT levels decreased significantly after surgery and antibiotic therapy. However, as far as we know, only a previous study¹⁴ has compared the effectiveness for the diagnostic discrimination between NF and cellulitis using PCT levels and LRINEC score. That study included only 3 patients with NF who presented an LRINEC of 6–8 points, but 5 of the 21 patients with

cellulitis also had scores of 6 or more points, while the PCT level was significantly higher in patients with NF.

Other variables related to the diagnosis of NF have been analyzed in other studies. Wang and Hung¹⁵ found a significant association for oxygen saturation <70% in patients with NF. Zahar et al.¹⁶ found an association only between clinical variables and the diagnosis of NF.

This study has several limitations, reason why its results should be taken with caution. The study had the inherent weaknesses of a retrospective observational study for potential bias in patient selection. Moreover, the sample size was relatively small, but similar to the majority of the published studies, due to the low prevalence of the disease. The cut-off point of the PCT level 0.87 ng/ml was relatively low. Therefore, we thought it should be assessed in the context of clinical signs. Nonetheless, it was found that the PCT-based risk scale was effective for the differential diagnosis between NF and cellulitis. Although these findings seem promising and useful in clinical practice, further comparative and larger studies are necessary to confirm these results.

In conclusion, in this study, measuring the PCT serum level was a more effective method than LRINEC score to early discriminate between NF and cellulitis of the limbs. A low level of PCT, associated with the signs and symptoms and physical examination, is especially useful to rule out the early diagnosis of NF.

Conflict of interest

The authors report no conflict of interest.

References

- Bucca K, Spencer R, Orford N, Cattigan C, Athan E, McDonald A. Early diagnosis and treatment of necrotizing fasciitis can improve survival: an observational intensive care cohort study. *ANZ J Surg*. 2013;83:165–370.
- Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med*. 2004;32:1535–41.
- Bechar J, Sepehrpour S, Hardwicke J, Fillobos G. Laboratory risk indicator for necrotizing fasciitis (LRINEC) score for the assessment of early necrotizing fasciitis: a systematic review of the literature. *Ann R Coll Surg Engl*. 2017;99:341–6.
- Kincius M, Telksnys T, Trumbeckas D, Jievaltas M, Milonas D. Evaluation of LRINEC scale feasibility for predicting outcomes of Fournier gangrene. *Surg Infect (Larchmt)*. 2016;17:448–53.
- Wilson MP, Schneir AB. A case of necrotizing fasciitis with a LRINEC score of zero: clinical suspicion should trump scoring systems. *J Emerg Med*. 2013;44:928–31.
- Holland MJ. Application of the laboratory risk indicator in necrotizing fasciitis (LRINEC) score to patients in a tropical tertiary referral centre. *Anaesth Intensive Care*. 2009;37:588–92.
- Su Y, Chen H, Hong Y, Chen C, Hsiao C, Chen I. Laboratory risk indicator for necrotizing fasciitis score and the outcomes. *ANZ J Surg*. 2008;78:968–72.
- Foo RM, Tung ML, Poon LM, Chan D, Smitasin N, Koh LP, et al. Necrotizing fasciitis in hematological patients: enterobacteriaceae predominance and limited utility of laboratory risk indicator for necrotizing fasciitis score. *Open Forum Infect Dis*. 2015;2, <http://dx.doi.org/10.1093/ofid/ofv081>, ofv081.
- Mehanic S, Baljic R. The importance of serum procalcitonin in diagnosis and treatment of serious bacterial infections and sepsis. *Mater Sociomed*. 2013;25:277–81.
- Al-Thani H, el-Menyar A, Shaikh N, Mudali I, Mekhodathil A, Asim M, et al. Risk stratification of necrotizing fasciitis based on the initial procalcitonin concentration: a single center observational study. *Surg Infect (Larchmt)*. 2015;16:806–12.
- Ballesteros-Betancourt J, García-Tarriño R, Ríos-Guillermo J, Rodríguez-Roiz J, Camacho P, Zumbado-Dijeres A, et al. Infecciones necrosantes de partes blandas atendidas en un servicio de urgencias de tercer nivel: evolución y correlación con la escala Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC). *Rev Esp Cir Ortop Traumatol*. 2017;61:265–72.
- Linscheid P, Seboek D, Nylén ES, Langer I, Schlatter M, Becker KL, et al. In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. *Endocrinology*. 2003;144:5578–84.
- Friederichs J, Hutter M, Hierholzer C, Novotny A, Friess H, Bühren V, et al. Procalcitonin ratio as a predictor of successful surgical treatment of severe necrotizing soft tissue infections. *Am J Surg*. 2013;206:368–73.
- Kato T, Fujimoto N, Honda S, Fujii N, Shirai M, Nakanishi T, et al. Usefulness of serum procalcitonin for early discrimination between necrotizing fasciitis and cellulitis. *Acta Derm Venereol*. 2017;97:141–2.
- Wang TL, Hung CR. Role of tissue oxygen saturation monitoring in diagnosing necrotizing fasciitis of the lower limbs. *Ann Emerg Med*. 2004;44:222–8.
- Zahar JR, Goveia J, Lesprit P, Brun-Buisson C. Severe soft tissue infections of the extremities in patients admitted to an intensive care unit. *Clin Microbiol Infect*. 2005;11:79–82.
- Tang WM, Ho PL, Fung KK, Yuen KY, Leong JC. Necrotizing fasciitis of a limb. *J Bone Joint Surg Br*. 2001;83:709–14.
- Tsai YH, Hsu RW, Huang KC, Chen CH, Cheng CC, Peng KT, et al. Systemic *Vibrio* infection presenting as necrotizing fasciitis and sepsis. A series of thirteen cases. *J Bone Joint Surg Am*. 2004;86A:2497–502.
- Cheng NC, Tai HC, Tang YB, Chang SC, Wang JT. Necrotizing fasciitis: clinical features in patients with liver cirrhosis. *Br J Plast Surg*. 2005;58:702–7.
- Ozalay M, Ozkoc G, Akpınar S, Hersekli MA, Tandogan RN. Necrotizing soft-tissue infection of a limb: clinical presentation and factors related to mortality. *Foot Ankle Int*. 2006;27:598–605.
- Tsai YH, Hsu RW, Huang TJ, Hsu WH, Huang KC, Li YY, et al. Necrotizing soft-tissue infections and sepsis caused by *Vibrio vulnificus* compared with those caused by *Aeromonas* species. *J Bone Joint Surg Am*. 2007;89:631–6.
- Cheng NC, Su YM, Kuo YS, Tai HC, Tang YB. Factors affecting the mortality of necrotizing fasciitis involving the upper extremities. *Surg Today*. 2008;38:1108–13.
- Hankins CL, Southern S. Factors that affect the clinical course of group A beta-haemolytic streptococcal infections of the hand and upper extremity: a retrospective study. *Scand J Plast Reconstr Surg Hand Surg*. 2008;42:153–7.
- Chee E, Kwan M, Khoo E. Necrotizing fasciitis of the lower limb – a prospective study of prognostic factors affecting mortality. *Malays Orthop J*. 2009;3:32–5.
- Khanna AK, Tiwary SK, Kumar P, Khanna R, Khanna A. A case series describing 118 patients with lower limb necrotizing fasciitis. *Int J Low Extrem Wounds*. 2009;8:112–6.
- Yeung YK, Ho ST, Yen CH, Ho PC, Tse WL, Lau YK, et al. Factors affecting mortality in Hong Kong patients with upper limb necrotizing fasciitis. *Hong Kong Med J*. 2011;17:96–104.
- Tsai YH, Wen-Wei Hsu R, Huang KC, Huang TJ. Comparison of necrotizing fasciitis and sepsis caused by *Vibrio vulnificus* and *Staphylococcus aureus*. *J Bone Joint Surg Am*. 2011;93:274–84.
- Espandar R, Sibdari S, Rafiee E, Yazdani S. Necrotizing fasciitis of the extremities: a prospective study. *Strategies Trauma Limb Reconstr*. 2011;6:121–5.
- Chen IW, Yang HM, Chiu CH, Yeh JT, Huang CH, Huang YY. Clinical characteristics and risk factor analysis for lower-extremity amputations in diabetic patients with foot ulcer complicated by necrotizing fasciitis. *Medicine (Baltimore)*. 2015;94:e1957.
- Lee CY, Li YY, Huang TW, Huang TY, Hsu WH, Tsai YH, et al. Synchronous multifocal necrotizing fasciitis prognostic factors: a retrospective case series study in a single center. *Infection*. 2016;44:757–63.
- Corona PS, Erimeiku F, Reverte-Vinaixa MM, Soldado F, Amat C, Carrera L. Necrotizing fasciitis of the extremities: implementation of new management technologies. *Injury*. 2016;47:66–71.