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● *Original Contribution*

THE RELATIONSHIP BETWEEN FLUID ACCUMULATION IN ULTRASONOGRAPHY AND THE DIAGNOSIS AND PROGNOSIS OF PATIENTS WITH NECROTIZING FASCIITIS

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Abstract—Necrotizing fasciitis is a severe soft-tissue infection with a high mortality rate. There is little literature on the relationship between the ultrasonographic finding of fluid accumulation along the deep fascia and the diagnosis and prognosis of necrotizing fasciitis. This retrospective study showed that when fluid accumulation was present along the deep fascia, patients with clinically suspected necrotizing fasciitis had a higher probability of having necrotizing fasciitis. The ultrasonographic finding of fluid accumulation with a cutoff point of more than 2 mm of depth had the best accuracy (72.7%) for diagnosing necrotizing fasciitis. In regard to the prognosis of necrotizing fasciitis, when fluid accumulation was present along the deep fascia, patients with necrotizing fasciitis had a longer length of hospital stay and were at risk of amputation or mortality. Ultrasonography is a point-of-care imaging tool that facilitates the diagnosis and prognosis of necrotizing fasciitis. (E-mail: ljnjohn@gmail.com)

Key Words: **Ultrasonography, Necrotizing fasciitis, Diagnosis, Prognosis, Fluid accumulation.**

INTRODUCTION

Necrotizing fasciitis (NF) is a severe soft-tissue infection with a fulminant progression and high mortality rate, even with modern medical devices. The reported mortality rate is 19.3% (Khamnuan et al. 2015). Early surgical intervention may significantly reduce this rate (McHenry et al. 1995; Voros et al. 1993). Thus, early diagnosis of NF is very important for early surgery and a better patient outcome.

The clinical presentation of NF includes fever, toxicity, severe pain out of proportion to skin findings, crepitus, rapid progression, skin bullae, necrosis or ecchymosis (Stevens et al. 2014). The definitive diagnosis of NF is obtained through exploration of the tissues, but this method is invasive.

Radiographic imaging studies can determine the severity and depth of soft-tissue infection, including ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). Although CT and MRI have good diagnostic value in NF (Fernando et al. 2018; Kehrl 2014), CT and MRI might not be rapidly available in the emergency department (ED), especially when the unit is crowded. In our experience, if we arrange for a CT or an MRI in the ED, it may take a few hours waiting before results are available. Alternatively, ultrasonography could be done a few minutes after the patient has visited the ED. Radiographic imaging studies should not delay surgery (Zumla 2010). Ultrasonography is a convenient, cost-effective and non-invasive tool, and its utility may enable prompt diagnosis of NF, although CT and MRI may subsequently indicate negative results (Kehrl 2014).

The ultrasonographic findings of NF may include irregularity or thickening of the deep fascia, abnormal fluid collection along the deep fascial plane and subcutaneous emphysema (Castleberg et al. 2014; Tsai et al. 1996; Wronski et al. 2011). The use of fluid accumulation of more than 4 mm in depth along the deep fascial layer was shown to have a high sensitivity (88.2%) and specificity (93.3%) (Yen et al. 2002). However, there is little literature discussing the relationship between the ultrasonographic finding of fluid accumulation along the

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deep fascia and the prognosis of NF. The improved prediction of prognosis might help physicians to explain the severity of the disease and accelerate early surgical intervention. The purpose of this study is to evaluate the relationship between the ultrasonographic finding of fluid accumulation along the deep fascia and the diagnosis and prognosis of NF.

MATERIALS AND METHODS

This retrospective study with prospective enrollment was conducted in one suburban, academic, tertiary care hospital with 1,300 beds and approximately 80,000 annual ED visits. The study was approved by the institutional review board. Informed consent was required for the study protocol. The study enrolled adult patients who had clinically suspected NF of the limbs and visited the ED from February 2015 to November 2016. Patients who were younger than 18 y of age, had previously received antibiotics or debridement or had lesions involving the trunk area were excluded. The clinical suspicion of NF of the limbs was based on symptoms and clinical signs, including severe pain out of proportion to the skin findings, rapid progression, crepitus, skin bullae, necrosis or ecchymosis. All enrolled patients received ultrasonography within 1 h after ED arrival. After laboratory data had been obtained, we consulted orthopedic surgeons for surgical opinion. The study endpoint was when patients were discharged from the ward. The enrolled patients were divided into two groups according to the discharge diagnosis: The NF group and the non-NF group. Patients of the NF group had the final ward diagnosis of NF, which was confirmed by pathology report after surgical intervention. Patients who did not have surgical intervention or whose pathology report didn't support the diagnosis of NF were classified to the non-NF group.

Ultrasound scans were obtained for all patients included in the study. Ultrasound images were obtained with standard ultrasound systems (Philips Clear Vue 550, Philips Healthcare, Bothell, WA, USA) equipped with 4−12 MHz linear probes by three experienced operators. These operators were emergency physicians who received 8-h basic and soft-tissue ultrasonographic training before the study. To test the inter-rater reliability, these emergency physicians simultaneously rated whether ultrasonographic findings of NF were present or not on 10 patients with soft-tissue infections in the ED. The inter-rater reliability was 100%. Ultrasonography was only performed from 7 AM to midnight, when these emergency physicians were available. All images were saved longitudinally. The ultrasonographic findings that we recorded include irregular or thickened fascia, subcutaneous emphysema, fluid accumulation among the deep fascia and the depth of fluid. We compared the lesion side with the contralateral, non-lesion side when saving the images (Fig. 1). Patients were excluded from our data if the non-lesion side had fluid accumulation like the lesion side.

The following demographic and clinical variables were recorded: age; sex; site of infection; comorbidities, including diabetes mellitus, hypertension, chronic hepatitis, liver

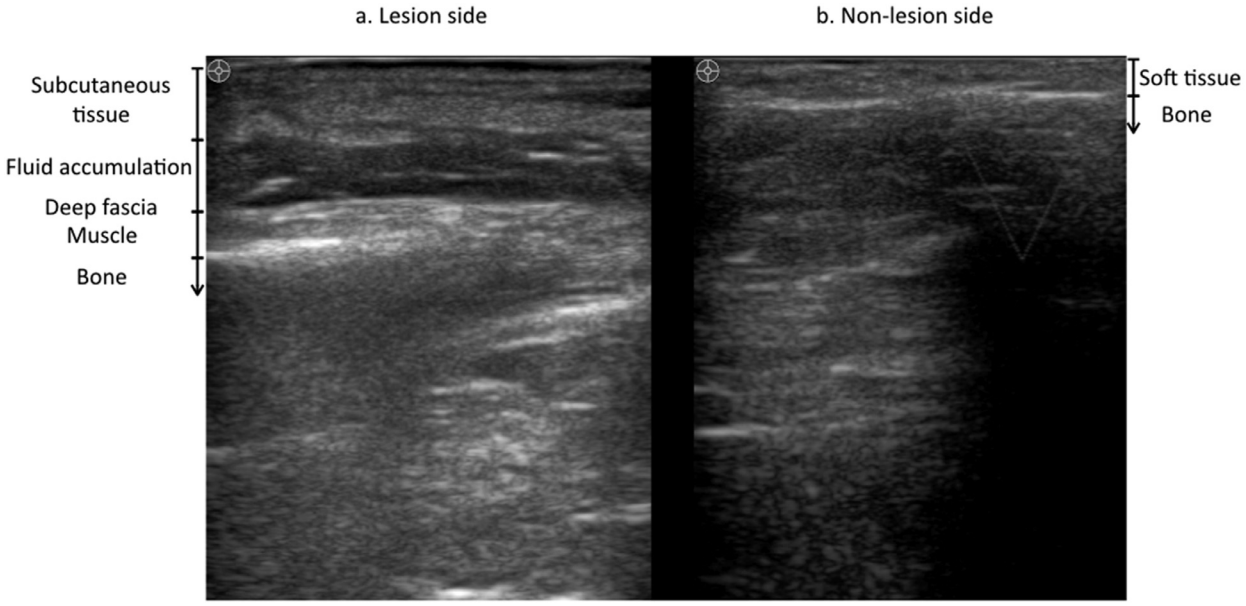

Fig. 1. Ultrasonography showing abnormal fluid accumulation in the deep fascial layer. This picture was obtained from bilateral hands. (a) Lesion side had clinically suspected NF. (b) Non-lesion side had normal skin appearance. NF = necrotizing fasciitis.

cirrhosis, chronic kidney disease, adrenal insufficiency, cancer, peripheral vascular disease and alcohol use disorder; length of stay; and mortality. We used SPSS to analyze the data. All variables were compared between the NF and non-NF groups. We used the X^2 test (or Fisher's exact test when appropriate) for proportions with dichotomous variables and the Mann−Whitney *U* test for medians with numerical variables. A p value < 0.05 was considered to indicate a significant difference. We tried to define a reasonable cutoff value of fluid accumulation for diagnosing NF using sensitivity, specificity and accuracy. We used the receiver operating characteristic (ROC) curve and the area under the curve (AUC) to evaluate the accuracy of the ultrasonographic measurement of fluid accumulation depth along the fascial layers for diagnosing NF.

RESULTS

There were 95 patients enrolled in our study, which were divided into NF (48 patients) and non-NF (47 patients) groups, with 68 male patients and 27 female patients (Fig. 2). Patients were classified to the non-NF group because they did not have surgical intervention or because their pathology reports didn't support the diagnosis of NF. Most patients in the non-NF group were diagnosed with cellulitis when they were discharged from the hospital.

For comorbidities between groups (Table 1), there was a higher prevalence of diabetes mellitus, liver cirrhosis and alcohol use disorder in the NF group. The NF group also had a longer length of stay in the hospital. There were four patients who died in the NF group, and all their deaths were caused by disease progression despite surgical intervention. Three of these four patients were younger than 70 y old. There were also two patients who died in the non-NF group: One died because of bacteremia with a blood culture pathogen that was different than the wound culture pathogen, and the other died because of pneumonia and subsequent respiratory failure. Both of these patients were older than 70 y old.

The NF ultrasonographic data are shown in in Table 2. We found that the fluid accumulation and the occurrence of an irregular or thickened fascial layer were significantly different between the NF and non-NF groups. Only three patients presented with subcutaneous emphysema, and all of them were in the NF group.

We analyzed the data using the ROC curve and AUC value (Fig. 3). AUC was 0.774, and the 95% confidence interval was 0.679−0.869. The best cutoff point of fluid accumulation to diagnose NF was 2 mm (Table 3), which

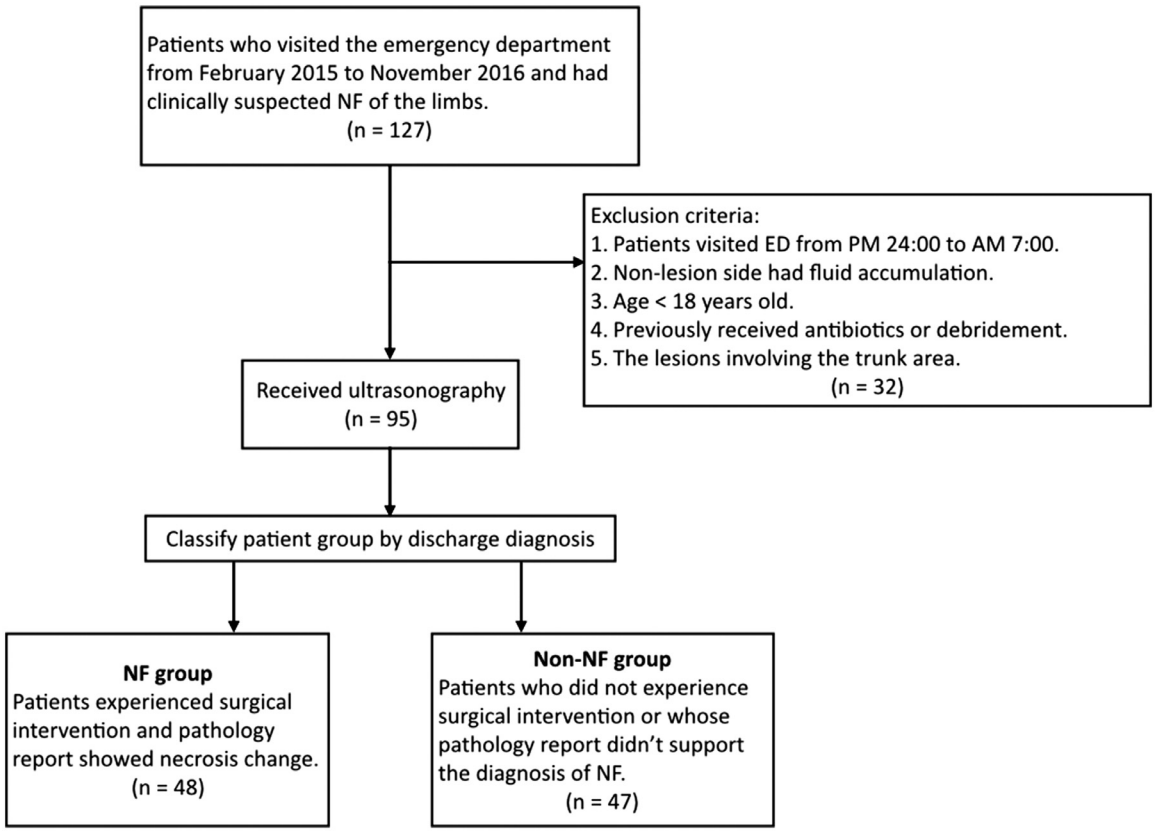

Fig. 2. Flow chart for patient groups. ED = emergency department; NF = necrotizing fasciitis.

Table 1. Epidemiology of patients with clinically suspected necrotizing fasciitis

Patient characteristics	NF (n = 48)	Non-NF (n = 47)	*p* Value
Age, y*	66 (19–94)	69 (34–89)	0.715
Male†	32 (66.7)	36 (76.6)	0.283
Comorbidities†			
Diabetes mellitus‡	23 (47.9)	13 (27.7)	0.042
Chronic hepatitis	15 (31.3)	12 (25.5)	0.537
Liver cirrhosis‡	9 (18.8)	1 (2.1)	0.015
Chronic kidney disease	16 (33.3)	10 (21.3)	0.188
Adrenal insufficiency	3 (6.3)	0 (0)	0.242
Cancer	7 (14.6)	1 (2.1)	0.059
Hypertension	27 (56.3)	23 (48.9)	0.475
Alcoholism‡	15 (31.3)	6 (12.8)	0.030
Location of infection†			
Upper limbs	14 (29.2)	7 (14.9)	0.094
Lower limbs	34 (70.8)	40 (85.1)	0.094
Prognosis			
Length of stay, d*,‡	36 (3–71)	8 (4–39)	<0.001
Mortality†	4 (8.3)	2 (4.3)	0.677

NF = necrotizing fasciitis.
* The data are given as the median with the range in parentheses.
† The data are given as the number of patients with the percentage in parentheses.
‡ $p < 0.05$.

Table 2. Ultrasonographic findings of patients with clinically suspected necrotizing fasciitis

Ultrasonographic findings*	NF n = 48	Non-NF n = 47	*p* Value
Fluid accumulation†	41 (85.4)	26 (55.3)	0.001
Irregular or thickened fascia‡	32 (66.7)	21 (44.7)	0.031
Subcutaneous cobblestone	8 (15.4)	12 (25.5)	0.289
Subcutaneous emphysema	3 (5.9)	0 (0)	0.242

NF = necrotizing fasciitis.
* Data are given as the number of patients with the percentage in parentheses.
† Fluid accumulation along the deep fascial layer compared with the same position on the contralateral normal limb.
‡ Irregular or thickened deep fascial layer.

had the best accuracy (72.7%) with a sensitivity of 75%, a specificity of 70.2%, a positive predictive value (PPV) of 71.7% and a negative predictive value (NPV) of 72.7%.

To assess the value of ultrasonography for determining the prognosis of NF patients, we compared the length of stay, number of operations, amputations and mortality, which are listed in Tables 4 and 5. The NF patients with fluid accumulation had a longer length of stay than NF patients without fluid accumulation (average: 39 d vs. 23 d). All NF patients who had an amputation or died had fluid accumulation (sensitivity and NPV 100%).

DISCUSSION

Our study showed that the ultrasonographic finding of fluid accumulation along the deep fascia may facilitate the diagnosis and prognosis of NF. The ultrasonographic finding of fluid accumulation with a cutoff point of more than 2 mm of depth along the deep fascia had an accuracy of 72.7% and could further aid the diagnosis of NF. In regard to the prognosis of NF, when fluid accumulation was present along the deep fascia, patients with NF had longer lengths of hospital stays and were at risk of amputation or mortality. Therefore, ultrasonography can be used as a point-of-care imaging tool to help clinicians make critical decisions on the diagnosis and prognosis of NF.

There was a significantly higher prevalence of NF in patients who had cirrhosis, diabetes mellitus and alcohol use disorder, as shown in Table 1. The reason might be that the patients who had cirrhosis or diabetes mellitus were immunocompromised. If immunocompromised patients have a soft-tissue infection, there might be a greater possibility of disease progression, including NF. Mortality between the NF and non-NF groups showed no significant difference, which might be because of the small number of patients in this study.

The fluid accumulation and the occurrence of an irregular or thickened fascial layer were common ultrasonographic findings in patients with clinically suspected NF and was significantly different between the NF and non-NF groups. These ultrasonographic findings were consistent with previous studies (Castleberg et al. 2014; Tsai et al. 1996; Wronski et al. 2011; Yen et al. 2002). They revealed that when fluid accumulation was present along the deep fascia, patients with clinically suspected NF had a higher probability of having NF (85.4% vs. 55.3%, $p = 0.001$). Only three patients presented with subcutaneous emphysema, and all of them were in the NF group. Thus, subcutaneous emphysema could be used as an important criterion in differentiating NF and non-NF patients.

According to Yen et al. (2002), using more than 4 mm of fluid accumulation had a high sensitivity (88.2%) and specificity (93.3%) in diagnosing NF. However, in our study, when we used 4 mm as the cutoff point in diagnosing NF, the sensitivity was 42.3%, the specificity was 93.6%, the PPV was 88%, the NPV was 59.5% and the accuracy was 66.7% (Table 3). Our NF patient group was larger than that in the study by Yen et al. (48 vs. 17). The different results between our study and Yen's study might be due to a different prevalence of bacteria, which may lead to different clinical pictures. Most of our patients came from the south of Taiwan, but the patients in the other study were enrolled from the north of Taiwan. The prevalence of bacteria would be different because of the different locations and environments.

In regard to the prognosis of NF, our study found that the patients with NF who had fluid accumulation had longer lengths of stays than patients with NF who did not have fluid accumulation, and all patients with NF who had an

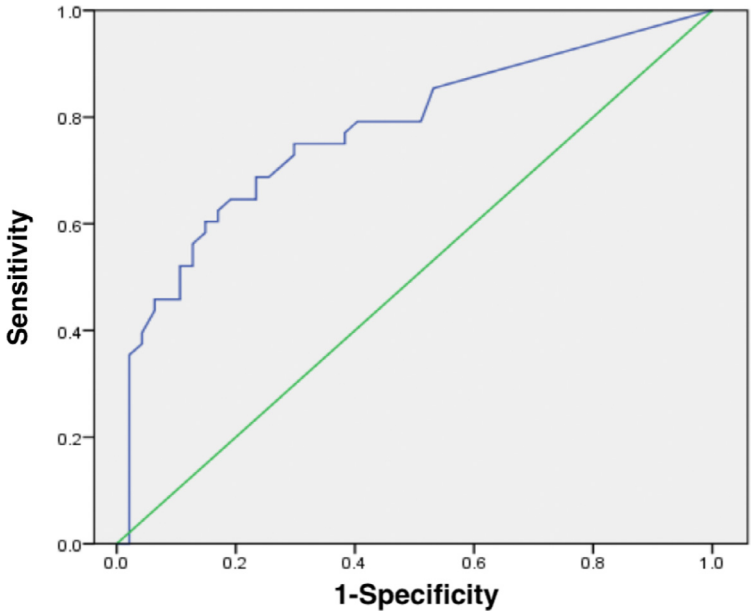

Fig. 3. The ultrasonographic findings of the fluid accumulation depth in the fascial layer for diagnosing NF. The AUC value was 0.774, and the 95% CI was 0.679−0.869. AUC = area under the curve; CI = confidence interval.

Table 3. The sensitivity, specificity and accuracy of diagnosis of necrotizing fasciitis by the depth of fluid accumulation on ultrasonography

Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
1 mm	86.5	48.9	65.2	76.7	68.7
2 mm	75.0	70.2	71.7	72.7	72.7
3 mm	55.8	85.1	80.6	63.5	69.7
4 mm	42.3	93.6	88.0	59.5	66.7
5 mm	19.2	97.9	90.9	52.3	56.6

NPV = negative predictive value; PPV = positive predictive value.

Table 4. Relationship between the ultrasonographic finding of fluid accumulation and the prognosis of patients with necrotizing fasciitis

	Fluid accumulation		
	No (n = 7)	Yes (n = 41)	*p* Value
Length of stay, d*	23 (15−34)	39 (3−71)	0.037
Number of operations*	2 (2−3)	3 (1−6)	0.102

* Data are given as the median with the range in parentheses.

amputation or died had fluid accumulation. Our study revealed that when fluid accumulation was present along the deep fascia, patients with NF had longer lengths of hospital stays and were at risk of amputation or mortality. Therefore, ultrasonography might help physicians to explain the severity of the disease and accelerate early surgical intervention.

There were some limitations to our study. First, the patient number was limited because NF is not a highly prevalent disease. However, our patient number was larger than previous studies investigating ultrasonographic findings for the diagnosis of NF. Second, the patients enrolled in our study only suffered from soft-tissue infections of the limbs. Finally, our patients came from the south of Taiwan, and there might be a different prevalence of bacteria and different clinical presentations for patients from different places. In the future, larger patient numbers are needed to obtain better accuracy on the utility of ultrasonography to diagnose NF and predict outcomes.

CONCLUSIONS

For the diagnosis of NF, when fluid accumulation was present along the deep fascia on ultrasound, patients with clinically suspected NF had a higher probability of having NF. The ultrasonographic finding of fluid accumulation with a cutoff point of more than 2 mm of depth may aid in diagnosing NF. For the prognosis of NF, when fluid accumulation was present along

Table 5. Relationship between the ultrasonographic finding of fluid accumulation and the prognosis of patients with necrotizing fasciitis

	Cases*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Amputation	3 (6.3)	100	15.6	7.3	100
Mortality	4 (8.3)	100	15.9	9.8	100

* Data are given as the number of patients with the percentage in parentheses.

the deep fascia on ultrasound, patients with NF had longer lengths of hospital stays and were at risk of amputation or mortality. Ultrasonography is a point-of-care imaging tool that facilitates the diagnosis and prognosis of NF.

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