ORIGINAL RESEARCH

Necrotizing fasciitis: risk factors of mortality

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Background: Necrotizing fasciitis (NF) is a serious infection of skin and soft tissues that rapidly progresses along the deep fascia. It becomes a fatal soft tissue infection with high mortality rate if treatment is delayed. Early diagnosis for emergency surgical debridement and broad-spectrum antibiotic therapy were the optimal treatments to reduce the mortality rate of NF.

Objective: The aim of this study was to identify risk factors that increased the mortality rate in patients with NF under routine clinical practices.

Methods: A retrospective cohort study was performed at three general hospitals located in northern Thailand. All medical records of patients with surgically confirmed NF treated between January 2009 and December 2012 were reviewed. Clinical predictors for mortality were analyzed using multivariable risk regression analysis.

Results: Of a total of 1,504 patients with a diagnosis of NF, 19.3% (n=290) died in hospital and 80.7% (n=1,214) survived. From multivariable analysis, being female (risk ratio [RR] =1.37, 95% confidence interval [CI] =1.01–1.84); age >60 (RR =1.39, 95% CI =1.25–1.53); having chronic heart disease (RR =1.64, 95% CI =1.18–2.28), cirrhosis (RR =2.36, 95% CI =1.70–3.27), skin necrosis (RR =1.22, 95% CI =1.15–1.28), pulse rate >130/min (RR =2.26, 95% CI =1.79–2.85), systolic BP <90 mmHg (RR =2.05, 95% CI =1.44–2.91), and serum creatinine ≥1.6 mg/dL (RR =3.06, 95% CI =2.08–4.50) were risk factors for mortality.

Conclusion: Prognostic factors for mortality in NF patients included being female; age >60; or having chronic heart disease, cirrhosis, skin necrosis, pulse rate >130/min, systolic BP <90 mmHg, and serum creatinine ≥1.6 mg/dL. Thus, disease progression to mortality may occur in such patients presenting one of these risk factors. Further examination or close monitoring for systemic involvement may be advantageous to reduce morbidity and mortality.

Keywords: clinical predictors, risk factor, mortality, necrotizing fasciitis

Introduction

Necrotizing fasciitis (NF) is commonly known as flesh-eating disease. The infection involves necrosis of the subcutaneous tissue and fascia first described by Wilson in the 1950s.[1] NF is a disease characterized by a rapidly progressing destruction of tissue and systemic toxicity, and delayed treatment can lead to an infection with a high mortality rate.[2] The incidence of NF has been varyingly reported worldwide, 0.4 cases per 100,000 population in Canada[3] and 1.3 cases per 100,000 population in Florida, USA.[4] The mortality rates reported of 15% to 36% in Ohio, USA (1989–1994);[5] Taiwan (1995–2006);[6] Chicago, USA (1999–2002);[7] and the Philippines (2004–2007).[8] In northern Thailand, Hongladaromp et al[9] reported the incidence of NF was 7.45 cases per 100,000 population, and the mortality rate ranged from 5.9% to 22.1%.[9,10]

Emergency surgical debridement and broad-spectrum antibiotic therapy remain the most appropriate treatments to reduce the mortality rate of NF. Delayed recognition and treatment can cause the disease to progress and increases the risk of poor outcomes, so it is very important to diagnose the disease at an early stage and treat rapidly. Previous studies have reported independent risk factors for mortality among NF patients including being female,[11] having advanced age,[6,7,11–13] diabetes mellitus (DM),[4] heart disease,[14,15] liver cirrhosis,[6,12,15] serum creatinine level 2 mg/dL,[6,11,12,14] white blood cell count >30,000/mm³,[14] hypoalbuminemia,[8] presence of hemorrhagic bleb,[16,17] and skin necrosis.[17] All studies presented varying prevailing epidemiology and microbiology in each place.

The aim of this study was to evaluate risk factors for mortality in a large group of patients with NF from three general hospitals in northern Thailand undergoing routine clinical practices. From clinical findings the identified risk factors can then be used as predictors in order to assist surgeons into taking preventative measures at an early stage of NF. However, some clinical data were unavailable for this study such as anaerobic bacteria culture and some laboratory findings that might be possible risk factors to predict mortality.

Patients and methods

This study was a retrospective cohort study. The medical records of patients with surgically confirmed NF were registered between January 2009 and December 2012 at three general hospitals located in northern Thailand (Chiang Rai, KamphaengPhet, and Phayao Provinces).

NF was defined by the presence of extensive necrosis involving at least the fascia and subcutaneous tissue, including myonecrosis.[18] The gray necrotic fascia and myonecrosis were detected intraoperatively by surgeons and used to identically follow Practice Guidelines for the Diagnosis of Skin and Soft Tissue Infections by the Infectious Diseases Society of America.[19] The definition of mortality was death at admission or 28 days after surgical treatment. Clinical data and demographic characteristics including sex, age, body mass index (BMI), education, occupation, underlying disease, vital signs within the first day of admission and after 48–72 hours were retrieved from inpatient charts. Important data associated with the investigation and treatment of NF (wound appearance, site of infection, organisms involved, and laboratory data within the first day of admission and after 48–72 hours, surgical intervention, and outcome) were also extracted from the medical records.

In total 1,504 patients were enrolled in this study. All cases were assessed and treated with broad-spectrum antibiotics by emergency physicians. Patients were investigated, evaluated, and provided proper emergency surgical treatment. The surgical interventions included incision, drainage, debridement of the necrotic fascia or muscle, and amputation. All debris tissue was dissected, and in some of the cases tissue culture was performed. Anaerobic organism cultures were not performed because of the limitation of the culture process. Aerobic organism cultures were performed in some of the cases, but not all, depending on surgeon request. Although we have a standard practice guideline for taking tissue cultures or pus cultures in all infected specimens, some surgeons did not follow this guideline. The reasons were shortage of culture instruments or culture transferring process (loss of specimen). Furthermore, the data recording process in each provincial hospital was not good enough. Some of the important data such as tissue culture, blood culture, or pus culture might be lost.

Patients were divided into two groups: mortality and survival. Continuous variables were analyzed by Student's *t*-test or Wilcoxon rank sum test and assessed as mean or median with standard deviation or interquartile range, depending on the distribution of data. Differences in proportion were analyzed by Fisher's exact test and assessed as count and percentage. Firstly, the univariable risk regression generalized linear model and cluster hospitals were used to identify the possible independent risk factors for mortality. The clinically significant variables and all variables that have *P*-value less than 0.01 were included in the multivariable analysis model. Secondly, multivariable risk regression analysis with generalized linear model cluster hospitals and step-backward method were used to identify the independent risk factors for mortality. A *P*-value ≤0.05 was considered statistically significant.

This study was approved by the Ethics Committee of the Chiang rai Prachanukroh Hospital and Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Date of approved 22 January 2013 is number 032/2013, Research ID: 1461/Study Code: COM-13-1461-EX.

Results

The study enrolled 1,504 patients diagnosed with NF. The mortality rate was 19.3% (n=290) and the survival rate was 80.7% (n=1,214). Among the fatalities, 92.8% (n=269) died at admission and 7.2% (n=21) died after discharge from the hospital but within 28 days after surgery. Organisms cultured from blood and wounds are shown in Table 1. Blood cultures were performed in 428 (28.6%) of 1,502 patients. A positive isolated blood culture was found in 73 patients (17.1%). No bacteria were found in 355 patients (82.9%).

Table 1 Microorganisms in blood and wound cultures in patients with necrotizing fasciitis – comparison between mortality group and survival group

Organism	Mortality group		Survival group	
	Blood	**Wound**	**Blood**	**Wound**
Gram positive				
Staphylococcus aureus	3 (2.2)	13 (9.9)	2 (0.7)	76 (12.8)
Coagulase negative staphylococcus	4 (2.9)	6 (4.6)	8 (2.8)	20 (3.4)
Staphylococcus epidermidis	3 (2.2)	3 (2.3)	5 (1.7)	6 (1.0)
Staphylococcus saprophyticus	2 (1.5)	2 (1.5)	1 0.3	9 (1.5)
Streptococcus pyogenes	5 (3.7)	30 (22.9)	6 (2.1)	94 (15.9)
Streptococcus pneumoniae	1 (0.7)	2 (1.5)	2 (0.7)	1 (0.2)
Other gram positive	5 (3.7)	2 (1.6)	5 (1.7)	21 (3.6)
Gram negative				
Acinetobacter spp.	2 (1.5)	15 (11.5)	1 (0.3)	24 (4.0)
Stenotophomonas spp.	0 (0.0)	1 (0.8)	1 (0.4)	1 (0.2)
Salmonella spp.	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.2)
Citrobacter spp.	0 (0.0)	4 (3.1)	2 (0.7)	14 (2.4)
Escherichia coli	5 (3.7)	18 (13.7)	1 (0.3)	32 (5.4)
Other gram negative	11 (8.2)	28 (21.4)	6 (2.1)	99 (16.8)

Notes: There were no statistically significant differences in organisms in either blood culture or wound culture between both groups (*P*-value >0.05). Values are n (%).

Wound cultures were performed in 729 (48.5%) of 1,503 patients. Positive isolated specimens comprised 469 patients (64.3%), and negative ones comprised 260 patients (35.7%). Data for two patients in blood culture and one patient in wound culture were omitted owing to a lack of medical records. Blood culture was performed in 144 patients (9.6%), wound culture was performed in 450 patients (29.9%), and both blood and wound cultures were performed in 285 patients (19.0%). Overall cultures were done in 879 patients (58.4%). Data for two patients who had blood cultures and one patient who had a wound culture were omitted owing to a lack of medical records. The number of patients who had mixed infected organism (gram positive organism and gram negative organism) in the wound culture or the blood culture were 39 patients (5.3%) and 3 patients (0.7%), respectively. The number of patients who have multiple infected organism (more than one gram positive or gram negative organism) in wound culture and blood culture are 47 patients (6.4%) and 3 patients (0.7%), respectively. *Streptococcus pyogenes* was the most common gram positive organism in both blood culture (3.7%) and wound culture (22.9%) in the mortality group and in both blood culture (2.1%) and wound culture (15.9%) in the survival group. The overall percentage of *S. pyogenes* infection was 43.2% in the mortality group and 39.2% in the survival group. *Escherichia coli* was the most common gram negative organism in both blood culture (3.7%) and wound culture (13.7%) in the mortality group and wound culture (5.4%) in the survival group. The overall percentage of *E. coli*

infection was 17.8% in the mortality group and 27.4% in the survival group. However, there were no statistically significant differences in infected organism in either blood culture or wound culture between both groups (*P*-value >0.05).

Different characteristics between the groups included sex, age, BMI, education, occupation, underlying morbidity such as chronic heart disease, cirrhosis, hypertension, gout, and wound appearance such as erythema, hemorrhagic bleb, severe pain and site of infection, as shown in Table 2. This table demonstrates that female sex age more than 60 years, patients who have no education, or elderly patients who stay at home most of the time are risk factors for mortality in NF patients by univariable analysis. Most of the laboratory findings and vital signs either on admission or within 48–72 hours after admission of patients in the mortality group were statistically significantly worse than those in the survival group; they include higher polymorphonuclear cell (PMN) predominant, higher serum creatinine, lower bicarbonate (more acidosis), lower total serum protein, higher pulse rate, and lower systolic blood pressure. Furthermore, the number of patients in the mortality group presenting with severe sepsis was significantly higher than that in the survival group, as shown in Table 3.

The clinically significant variables such as skin necrosis and all variables that have *P*-value of less than 0.01 are included in the multivariable analysis model. Multivariable risk regression analysis with generalized linear model cluster hospitals and step-backward method demonstrated that the predictors of mortality among patients with NF were being female (risk ratio [RR] =1.37, 95% confidence interval [CI] =1.01–1.84, *P*=0.038), age >60 (RR =1.39, 95% CI =1.25–1.53, *P*<0.001), having chronic heart disease (RR =1.64, 95% CI =1.18–2.28, *P*=0.003), cirrhosis (RR =2.36, 95% CI =1.70–3.27, *P*<0.001), skin necrosis (RR =1.22, 95% CI =1.15–1.28, *P*<0.001), pulse rate >130/min (RR =2.26, 95% CI =1.79–2.85, *P*<0.001), systolic blood pressure <90 mmHg (RR =2.05, 95% CI =1.44–2.91, *P*<0.001), and serum creatinine ≥1.6 mg/dL (RR =3.06, 95% CI =2.08–4.50, *P*<0.001), as shown in Table 4.

Discussion

NF is an important surgical infection, and there is a high incidence of it in Thailand, especially in the northern part, because people there are mainly farmers and laborers, most of them with low education and practicing low hygiene. Caring for wounds or preventing serious infection is still a problem in northern Thailand's health care system.

Table 2 Demographic characteristics and clinical manifestations in patients with necrotizing fasciitis – comparison between mortality group and survival group (n=1,504)

Characteristics	Mortality group (n=290)	Survival group (n=1,214)	P-value
Sex			0.006
Male	142 (49.0)	704 (58.0)	
Female	148 (51.0)	509 (42.0)	
Age (year)			<0.001
<60	91 (31.7)	599 (49.8)	
≥60	196 (68.3)	605 (50.2)	
BMI (kg/m^2)			0.025
≤18.50	30 (12.2)	166 (15.2)	
18.51–29.99	92 (37.6)	482 (44.2)	
≥30.00	123 (50.2)	443 (40.6)	
Education			<0.001
No education	178 (61.4)	474 (39.2)	
Primary education	109 (37.6)	652 (53.8)	
Secondary education	1 (0.3)	61 (5.0)	
Bachelor's degree or higher	2 (0.7)	24 (2.0)	
Occupation			<0.001
Elderly who stay at home	165 (56.9)	533 (43.9)	
Farmers/laborers	116 (40.0)	616 (50.8)	
Official	9 (3.1)	64 (5.3)	
Underlying morbidity			
Diabetes	80 (27.6)	306 (25.2)	0.411
Heart disease	40 (13.9)	56 (4.6)	<0.001
Renal disease	13 (4.5)	32 (2.6)	0.122
Cirrhosis	23 (7.9)	38 (3.1)	0.001
Hypertension	138 (47.6)	399 (32.9)	<0.001
Gout	48 (16.5)	99 (8.2)	<0.001
Chronic alcoholism	41 (14.1)	191 (15.7)	0.528
Wound appearance			
Swelling	233 (80.3)	1,008 (83.0)	0.302
Erythema	188 (64.8)	584 (48.1)	<0.001
Bleb	166 (57.2)	484 (39.9)	<0.001
Skin necrosis	84 (29.0)	318 (26.2)	0.338
Gangrene	8 (2.8)	29 (2.4)	0.675
Severe pain	266 (91.7)	1,048 (86.4)	0.014
Site of wound			0.015
Head and neck	0 (0.0)	8 (0.6)	
Trunk	11 (3.8)	17 (1.4)	
Upper limb	53 (18.3)	222 (18.3)	
Lower limb	216 (74.5)	943 (77.7)	
Fournier's gangrene	3 (1.0)	2 (0.2)	
Multiple sites	7 (2.4)	22 (1.8)	
Hospital			0.021
Chiang Rai	165 (56.9)	650 (53.5)	
KamphaengPhet	111 (38.3)	445 (36.7)	
Phayao	14 (4.8)	119 (9.8)	

Note: Values are n (%).
Abbreviation: BMI, body mass index.

Table 3 Laboratory findings, vital signs, treatment modalities, and outcome of treatment – comparison between mortality group and survival group (n=1,504)

Characteristics	Mortality group (n=290)	Survival group (n=1,214)	P-value
Laboratory on admission			
WBC (/mm^3)	15,992.3±10,783.4	17,126.4±8,718.6	0.002
PMN (%)	84.4±12.1	81.5±12.1	<0.001
Creatinine (mg/dL)	2.8±1.8	1.7±1.3	<0.001
Bicarbonate (mmol/L)	17.0±5.2	22.6±4.6	<0.001
Total protein (g/dL)	5.7±1.0	6.6±1.0	<0.001
Laboratory 48–72 hours			
WBC (/mm^3)	17,242.9±9,569.3	13,379.2±7,173.1	<0.001
PMN (%)	83.9±13.8	76.6±14.6	<0.001
Creatinine (mg/dL)	3.0±2.1	1.9±1.7	<0.001
Bicarbonate (mmol/L)	15.3±5.7	24.3±13.7	0.006
Total protein (g/dL)	5.3±1.0	6.0±1.3	0.001
Vital signs on admission			
Body temperature (°C)	37.3±0.9	37.3±0.9	0.317
Pulse (/min)	98.3±19.5	89.8±14.6	<0.001
Respiratory (/min)	20.0±7.5	20.2±2.1	0.512
Systolic blood pressure (mmHg)	104.0±25.6	120.3±22.9	<0.001
Diastolic blood pressure (mmHg)	62.8±16.2	72.0±13.8	<0.001
Vital signs 48–72 hours			
Body temperature (°C)	37.5±1.1	37.2±0.7	<0.001
Pulse (beats/min)	99.1±20.2	85.9±12.0	<0.001
Respiratory (breaths/min)	17.0±8.7	19.9±2.6	0.299
Systolic blood pressure (mmHg)	116.4±22.2	121.4±16.7	<0.001
Diastolic blood pressure (mmHg)	69.3±14.2	73.3±10.6	<0.001
Treatment and outcome			
I&D	5 (1.7)	40 (3.3)	0.183
Debridement	169 (58.3)	791 (65.2)	0.030
Fasciotomy	131 (45.2)	521 (43.0)	0.510
Amputation	28 (9.7)	99 (8.2)	0.411
Severe sepsis	185 (73.1)	54 (4.5)	<0.001
Length of hospital stay (day)	10.1 (18.1)	11.6 (11.0)	<0.001

Note: Values are mean ± standard deviation or n (%).
Abbreviations: WBC, white blood cell count; PMN, polymorphonuclear cell or neutrophil; I&D, incision and drainage.

NF is of surgical urgency with a high mortality rate, even with sufficient treatment, with the reported rate of mortality varying from 6% to 36%.[5–8,10] The overall mortality rate in this study was 19.3% (290 patients) of 1,504 patients. These patients had adverse outcomes, and although the cases were investigated and treated with broad-spectrum antibiotics by emergency physicians, these patients died rapidly from systemic inflammatory response syndrome (SIRS).[5] However, identification of independent risk factors of death could have had some effect on survival and could have assisted surgeons to counter these risk factors as much as possible to achieve a successful outcome of treatment in all patients.

Table 4 Independent predictors of mortality in patients with necrotizing fasciitis using multivariable analysis generalized linear model (n=1,504)

Risk factors	RR	95% CI	P-value
Female	1.37	1.01–1.84	0.038
Age >60	1.39	1.25–1.53	<0.001
Chronic heart disease	1.64	1.18–2.28	0.003
Cirrhosis	2.36	1.70–3.27	<0.001
Necrosis	1.22	1.15–1.28	<0.001
Pulse rate >130/min	2.26	1.79–2.85	<0.001
Systolic blood pressure <90 mmHg	2.05	1.44–2.91	<0.001
Creatinine ≥1.6 mg/dL	3.06	2.08–4.50	<0.001

Abbreviations: RR, relative risk ratio; CI, confidence interval.

At admission time, this study identified the following risk factors for mortality: being female; age >60 years; having chronic heart disease, liver cirrhosis, skin necrosis, pulse rate >130/min, systolic blood pressure <90 mmHg, and serum creatinine level ≥1.6 mg/dL, and these findings were similar to those of many previous studies.[4,7,11,12,14] In this study, sex affected the outcome of treatment and could predict mortality. Females were at greater risk for mortality. This study found that the number of females with a BMI ≥30 was significantly higher than that of males (74.6% versus 38.6%, P-value 0.004). A possible reason was that females have a greater amount of subcutaneous fat than men and are more easily prone to infection. Elliott et al[11] reviewed 198 patients between March 1985 and June 1993, and also found that being female was an independent predictor of death. However, some studies have reported that sex did not influence mortality.[7,14–16,20]

Elderly persons with or without underlying diseases, such as chronic heart disease and liver cirrhosis, are considered as having worse prognostic factors, similar to previous studies reporting that advanced age was associated with an increased risk of mortality.[6,7,12,13,21,22] This study found that being more than 60 years old increased the mortality rate significantly. However, some studies found that advanced age had no effect on mortality.[5,8,16,17] NF occurred frequently in patients with underlying diseases. Diabetes was the most frequent comorbidity in NF patients. Previous studies reported that poorly controlled DM in NF patients can cause adverse outcomes.[23–27] In this study, DM did not demonstrate association in terms of survival. We did not explore in detail blood glucose as this data could not be extracted from the patients medical records. One possible reason is that most of our patients might have well-controlled DM. Therefore, further study should be performed to establish the exact effect of DM on adverse outcome or survival in NF patients.

We also found that other underlying diseases such as chronic heart disease or liver cirrhosis were associated with higher mortality, as did previous studies.[6,12,14,15,28] Patients with liver cirrhosis have a higher sensitivity to infection than those without. The mechanism for increased mortality in cirrhotic patients with infection may be immunologic and mechanical. Abnormalities affect immunity in patients with cirrhosis featuring cellular immunity and humoral immunity, T lymphocyte and B lymphocyte dysfunctions caused by malnutrition.[29] The abnormal defensive mechanism could be caused by decreasing phagocytic activity of the reticuloendothelial system, impaired function monocyte and incomplete chemotaxis.[28] Moreover, we found that skin necrosis was associated with higher mortality as in previous studies.[17,30] Infection and toxin-producing bacteria can cause skin necrosis and multiple organ failure. All necrotic tissue, including fascia, must be removed by surgical debridement to reduce the bacteria, and broad-spectrum antibiotics should be administered promptly whenever NF is diagnosed.[31]

A pulse rate of more than 130 beats per minute and systolic blood pressure of less than 90 mmHg were also associated with increased mortality. The consequences of septic shock occurred in patients with severe systemic infection.[32] Septic shock was a typical complication in patients with NF.[33] In patients with septic shock, hypotension (a systolic blood pressure below 90 mmHg) was a significant risk factor for organ dysfunction and death, as reported in previous studies.[3,15,16,34] Clinical suspicion must lead to promptly maintained fluid resuscitation with intravenous broad-spectrum antibiotics and aggressive surgical debridement.[33] However, in patients with NF and septic shock, to maintain these changes in the circulation may lead to acute kidney failure and elevate serum creatinine.[35]

Referring to laboratory findings, increased serum creatinine has been an associated risk factor of death in NF, which has also been reported by many previous studies.[6,11,12,14,17] Increased creatinine levels can be used to predict impaired renal function most likely associated with septic shock, and may indicate renal failure. Acute renal failure in NF patients was a life-threatening condition when treatment was delayed or not cautious enough.[17] All patients with a confirmed, progressive increase in their serum creatinine level should consult with a nephrologist for dialysis.[36] Regarding the hospital variable, all the three hospitals are provincial hospitals, and, therefore, the health care system is the same with no difference in hospital conditions. Also, the mortality of NF did not differ among the hospitals. Although the P-value of the hospital variable is 0.021, we set a P-value of 0.01 as

statistically significant difference, and, therefore, there is no difference in mortality among the hospitals.

In the review of literature, prognostic tools to evaluate the severity of NF patients on admission included the LRINEC (laboratory risk indicator for NF) score, composed of six marker variables, including C-reactive protein, total white blood cell count, hemoglobin, serum sodium, serum creatinine, and serum glucose;[37] and APACHE II (acute physiology and chronic health evaluation II) scores were used as a prognostic scoring system for critical care including the patient's vital signs (temperature, mean arterial pressure, heart rate, and respiratory rate), oxygenation (A-PaO$_2$ [FiO$_2$ >50%] or PaO$_2$ [FiO$_2$ <50%]), metabolic parameters (sodium, potassium, creatinine, bicarbonate concentrations [Arterial pH or HCO$_3$], hematocrit, white blood cell count), and Glasgow coma score and calculates a score relating to severity of the disease of a patient who was admitted to the ICU.[38]

The limitations of this study include the following: we could not apply either of these scoring systems (LRINEC and APACHE II), because this study was a retrospective study, some important data could have been omitted because of insufficient medical records and laboratory limitations in provincial hospitals such as unexamined serum C-reactive protein arterial blood gas in all patients. Unfortunately, some data were not available in the clinical manifestations such as non-recorded Glasgow coma score.

Conclusion

Risk factors of mortality in patients with NF included being female; age >60 years; having chronic heart disease, liver cirrhosis, skin necrosis, pulse rate >130/min, systolic blood pressure <90 mmHg, and serum creatinine level ≥1.6 mg/dL. Thus, patients presenting any clinical predictors should direct concern toward progression of disease and might be considered for early investigation or close monitoring to prevent morbidity and mortality as much as possible. In addition, health care promotion should be directed toward preventing adverse events and early detection of NF.

Acknowledgments

Disclosure

The authors report no conflict of interest in this work.

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