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Center-based First-line Therapy Is a Significant Predictor for Mortality of Fournier Gangrene

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Introduction: Fournier gangrene is a life-threatening urological disease that requires rapid surgical intervention. Despite major improvements in medical therapy, the mortality of Fournier gangrene has not changed during the past 25 years. To potentially improve the outcome, we analyzed different medical processes for overall mortality in the treatment of Fournier gangrene.

Methods: We performed a retrospective single-center study of 21 patients with Fournier gangrene. Patients were grouped according to initial symptoms, first medical advice, blood tests, medical history, and further clinical processes and compared using a t test, χ^2 test, or Fisher exact test. A t test for heterogeneous variances was used if a Levene test showed significantly different variances, otherwise a t test for homogeneous variances was used. The log-rank test was applied for survival analysis. Logistic regression was applied to identify potential clinical predictors for mortality. Follow-up was performed until 130 days after the first surgical intervention.

Results: There were no significant differences in the mortality rate of patients depending on the day and time of presentation in the hospital. Of the patients first consulting a urologist (either outpatient or hospital), no patient died within the first 120 days. By contrast, approximately 70% of patients who were transferred by a hospital without urologic specialization or a nonurologic outpatient clinic ($P = .008$) died within the first 130 days after surgery. Multivariate survival analysis showed that the type of first doctor's advice could serve as a significant factor in determining patients' mortality ($P = .031$), which also correlated with a significantly shorter duration of the first surgical procedure (110 vs 54 minutes, $P = .019$).

Conclusion: Despite the small cohort, we were able to show a significant correlation between the initial doctor's advice, either by a urologist or nonurologist, and the patient's mortality. Considering the life-threatening potential of Fournier gangrene, professionals should develop strategies to educate nonurologists and raise awareness about this disease and its clinical presentation to optimize rapid intervention and reduce mortality.

Key Words: Fournier gangrene, first-line therapy, weekend effect

INTRODUCTION

Fournier gangrene is a life-threatening urological disease, which is defined as soft-tissue necrosis in the genitourinary tract, particularly in the perineum or perianal regions.[1] Initial management includes a combination of radical, immediate surgical debridement and intravenous administration of wide-spectrum antibiotics against polymicrobial infection.[2] Imaging before surgery of the abdomen and

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pelvis—primarily by computer tomography—can be considered to help planning surgical debridement.

Overall mortality of the disease is estimated at about 20%. So far, several risk factors such as diabetes, hypertension, and congestive heart failure have been reported for having an impact on mortality.[3] In addition, clinical monitoring parameters such as an increase in white blood cell or platelet count, FGSI Score (Fournier Gangrene Severity Score) >9, and mechanical ventilation have been shown to predict poor outcome.[4]

Despite major improvements in medical therapy, mortality due to Fournier gangrene has not changed during the past 25 years.[5]

To potentially improve patients' outcome, we analyzed different medical processes for overall mortality in the treatment of the Fournier gangrene at a German university hospital over the past 7 years.

Furthermore, we evaluated a potential *weekend effect* of Fournier gangrene. The *weekend effect* characterizes a higher rate of complications during medical procedures performed on the weekend.[6] It has first been reported in myocardial infarction, which was shown to have higher mortality when treated on weekends because of delayed conduction of coronary angiography.[7]

The *weekend effect* has also been shown in several other medical entities requiring immediate medical attention, such as strokes.[8] However, it has not yet been investigated in Fournier gangrene.

METHODS

Study Population

We conducted a retrospective, single center study of 21 patients, including all patients in our database who were ascribed with an ICD-10 code of N49.9 and treated at our hospital between 2014 and 2022. Basis of analysis was the medical report, laboratory values, and the discharge letter of the referring hospital/outpatient department.

Diagnosis was confirmed clinically, characterized by typical signs of Fournier gangrene, namely polymicrobial soft-tissue infection in combination with necrosis of the external genitalia or perineum. Patients without evidence of tissue necrosis were explicitly excluded to avoid any type of disproportion within our cohort. Local ethics committee approval of the University of Cologne was obtained.

Fournier Gangrene (Course of Disease)

Patients were grouped according to initial symptoms, blood tests, medical history, and further clinical processes (time span to consultation, duration of initial surgical and conservative management, etc). Follow-up was performed until 130 days after first surgical intervention. To investigate preclinical parameters, which might be associated with the therapeutic outcome, we analyzed onset of symptoms, first medical advice defined as the first recommendation by treatment, and time until admission to the hospital. To evaluate a potential existence of a weekend effect, we analyzed clinical processes and outcomes of patients presenting on weekdays vs those presenting on the weekend. Weekdays were defined as admissions between Monday 8 AM and Friday 4 PM while weekend admissions were defined as those between Friday 4 PM and Monday 8 AM.

Table 1. *Descriptive Statistic of the Cohort*

Clinical characteristic	Range	Median
Age (y)	15-75	56
<60	52.4%	
>60	47.6%	
Length of stay (d)	5-122	28
<30	57.1%	
>30	42.9%	
Duration of ICU treatment (d)	3-114	6
<30	80.1%	
>30	19.9%	
Number of operative debridement sessions	1-15	6
<5 sessions	38.1%	
≥5 sessions	61.9%	

ICU, intensive care unit.

Statistical Analysis

Statistical analysis was conducted using SPSS Statistics 25 (IBM Corp., Armonk, NY, USA) and R (R Core Team, 2022). The Student t test was used for comparing the means of the groups of survivors as compared with the deceased. Categorical data were analyzed using the Fisher exact test or χ^2 test. Survival analysis was conducted making use of the log-rank test. P-values were considered statistically significant at $P < .05$. All of them were 2-sided. Next, logistic regression was applied to identify potential clinical predictors before initial debridement for mortality.

RESULTS

Descriptive Statistics of the Cohort

All 21 patients enrolled (100%) were male while the age of patients was between 15 and 75 years (median: 56 years). Overall mortality was 38.1%, and duration of hospital care was between 5 and 122

Table 2. *Clinical Characteristics in the Group of Survived and Deceased*

Clinical characteristic	Survived n = 13	Deceased n = 8	P-value
Diabetes (%)	38.5	37.5	1[a]
Obesity (%)	15.4	50	.146[a]
Smoker (%)	46.2	37.5	1[a]
HIV (%)	—	—	—
Hypertension (%)	38.5	37.5	1[a]
Chronic kidney disease (%)	—	—	—
Chronic heart failure (%)	7.7	37.5	.253[a]
Malignant disease (%)	30.8	12.5	.606[a]
Alcohol abuse (%)	15.4	25	.713[a]
Days on intensive care unit (d)	10 ± 16	36 ± 44	.155[b]
Days of ventilation (d)	4 ± 6	10 ± 7	**.041**[b]
Number of surgeries	5 ± 4	8 ± 4	.319[b]

[a] Fisher exact test.
[b] Student t-test.

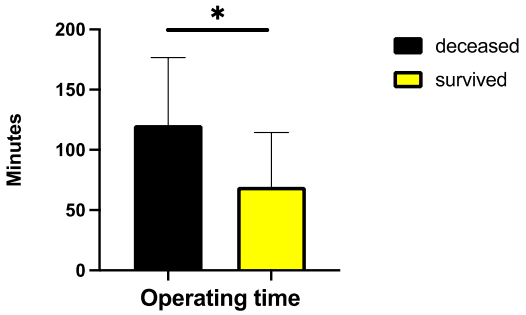

Figure 1. Duration of initial surgery in the group of deceased and survived. *Statistically significant.

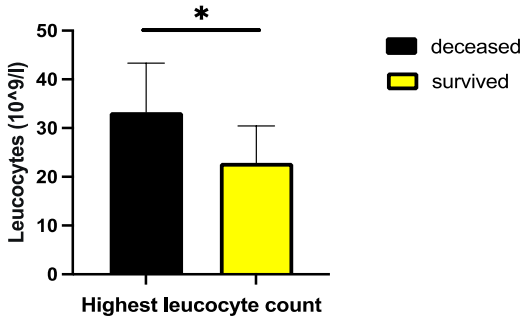

Figure 2. Highest leukocyte count during the clinical course. *Statistically significant.

days (median: 28 days). 71.4% of patients required treatment in the intensive care unit (ICU), the median duration of ICU treatment being 6 days. Number of debridement ranged between 1 and 15 (median: 6). 52.4% of the patients required negative pressure wound therapy (Table 1).

Medical History

No significant risk factors of mortality could be determined for medical history. However, although not significant, there was a trend toward higher mortality in overweight patients (Table 2).

Medical Processes

Despite given the fact that Fournier gangrene has an aggressive course of disease, the estimated duration from onset of symptoms until consultation to a doctor/hospital was longer in the patients' cohort, which survived. The time between consultation at our hospital and initial debridement was comparable in both groups ($P = .899$). The time period of initial debridement was significantly shorter among survivors, suggesting a correlation between duration of the disease and prognosis of patients ($P = .033$) (Figure 1; Table 3).

Laboratory Parameters

Next, we analyzed laboratory parameters at the time of admission to the hospital and during hospital stay. Initial inflammatory markers, blood count, and electrolytes were not significantly different between the examined groups of patients. Initial low platelet count ($P = .062$) and high serum urea ($P = .13$) seem to be associated with a higher risk of death.

During the hospital stay, a significantly higher number of leukocytes and lower nadir of hemoglobin were found in the group of deceased patients ($P = .014$ and $P = .019$, respectively) (Figures 2 and 3; Table 4).

Medical Processes After Debridement

Duration of stay in ICU varied between both groups, with a mean duration of 10 days in survivors vs 36 days in deceased patients, although the numerical difference was not statistically significant. The number of ventilation days was significantly shorter in the survivors' group, with a mean of 4 vs 10 days in the group of deceased patients ($P = .041$, Table 2). The total number of debridement procedures was comparable between the groups (Figure 4).

Because no patient within our cohort had died when initial consultation was performed by a urologist rather than a nonurologist ($P = .009$), we analyzed further aspects of the initial consultation. Operating time on the initial surgical debridement was significantly shorter ($P = .019$) when the initial consultation was provided by urologists compared with nonurologists, and consecutively, the maximum number of leukocytes during hospital stay was lower too ($P = .037$). Nevertheless, there was no difference

Table 3. *Medical Processes Before Surgery*

Medical process	Survived	Deceased	*P*-value
Time span from symptoms to consultation (min)	107 ± 63	57 ± 32	.125[a]
Time span from consultation at our hospital to initial debridement (min)	366 ± 349	388 ± 439	.899[a]
Operating time of initial debridement (min)	69 ± 45	120 ± 56	**.033**[a]

[a] Student *t*-test.

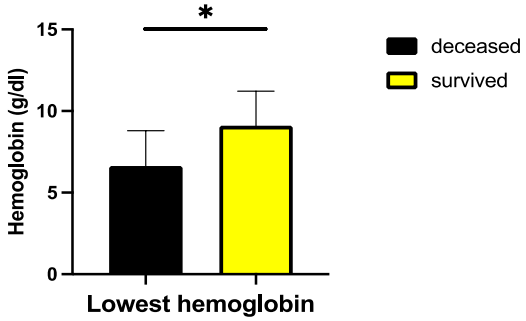

Figure 3. Lowest hemoglobin during the clinical course. *Statistically significant.

Table 4. *Laboratory Parameters of Survivors and Nonsurvivors*

Laboratory parameters	Survived	Deceased	*P*-value
Initial sodium (mmol/L)	131.8 ± 5.6	134.4 ± 5.7	.348[a]
Initial potassium (mmol/L)	4 ± 0.7	4.4 ± 1.1	.386[a]
Initial creatinine (mg/dl)	1.4 ± 0.9	2.5 ± 2.3	.193[a]
Initial leucocytes (10^9/L)	19.4 ± 8.6	20.9 ± 12.9	.761[a]
Initial platelets (10^9/L)	311.5 ± 174.4	184.5 ± 50.5	.062[a]
Initial albumine (g/L)	30.6 ± 11.3	27.8 ± 6	.61[a]
Initial urea (mg/dl)	57.3 ± 38.1	105.3 ± 94.7	.13[a]
Highest leukocyte count (10^9/L)	22.8 ± 7.6	33.3 ± 10.1	**.014**[a]
Highest CRP (mg/L)	310.7 ± 140.6	346.1 ± 120.4	.563[a]
Highest creatinine (mg/dl)	2.1 ± 2	3.3 ± 2.2	.219[a]
Highest LDH (U/L)	351.4 ± 112.9	490.7 ± 469.3	.46[a]
Lowest hemoglobin (g/dl)	9.1 ± 2.1	6.6 ± 2.1	**.019**[a]
Highest PCT (ug/L)	29 ± 48.2	52.6 ± 90.3	.453[a]

CRP, C-reactive protein; LDH, lactate dehydrogenase; PCT, procalcitonin.
[a] Student *t*-test.

concerning the duration of mechanical ventilation when comparing both groups ($P = .134$) (Figures 5-7; Table 5).

Weekend Effect in Fournier Gangrene

The weekend effect has been previously described in detail.[6] In our cohort, there was a slight tendency toward improved prognosis for patients treated during the week as opposed to those treated on weekends, although the difference was not statistically significant ($P = .142$) (Figure 8; Table 6).

Multivariate Analysis for Predictors of Mortality

A logistic regression approach was used to detect significant factors for mortality. We were mainly interested in the prediction of mortality after the first medical consultation, that is, either by a urologist or nonurologist. Lowest hemoglobin, highest leukocyte count, and days of ventilation had to be included as additional covariates because these variables showed a significant effect on mortality in the previous univariate analyses. A usual binary logistic regression could not be applied because a so-called complete separation was present, that is, the predictor "first medical advice" predicted mortality perfectly because no patient with a first medical advice died. Complete separation, as in this case, often occurs because of small sample sizes. Then, Firth bias-reduced logistic regression is an appropriate statistical approach.[9] Application of this regression method using the R package "logistf"[9] showed that only the predictor "first medical advice" had a significant effect on mortality ($P = .031$) (Table 7).

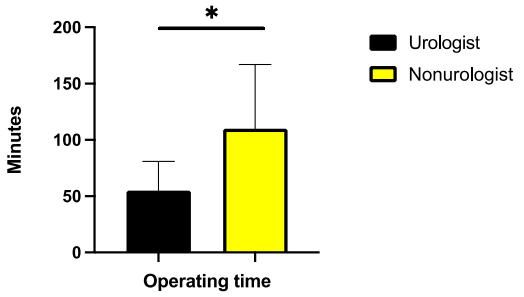

Figure 5. Operating time depending on the first medical advice. *Statistically significant.

DISCUSSION

Adequate and timely management of Fournier gangrene remains a challenge in daily clinical practice and has a high morbidity and mortality. Despite the enormous progresses of medical therapies, the mortality of Fournier gangrene still remains as high as about 20% and has not changed in the past few decades.[5] The objective of this study was to analyze clinical processes in the management of this life-threatening disease to potentially optimize the standard of care in Fournier gangrene.

Recently, Bowen et al[10] comprehensively reviewed all mortality predictors from high-volume centers over the past 2 decades. Our study confirmed not only delivery of mechanical ventilation per se as a risk factor, but also pointed out that the length of mechanical ventilation is an additional mortality predictor. In line with other studies, elevated white blood cell count and lower hemoglobin levels were associated with higher mortality. In contrast to Lauerman et al,[11] in our case series, a lower number of platelets was associated with higher mortality, likely a sign of incipient sepsis. Furthermore,

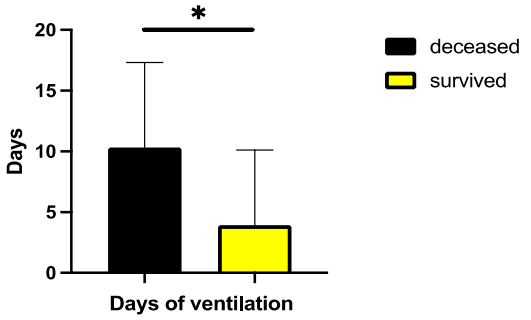

Figure 4. Days of ventilation in ICU. *Statistically significant.

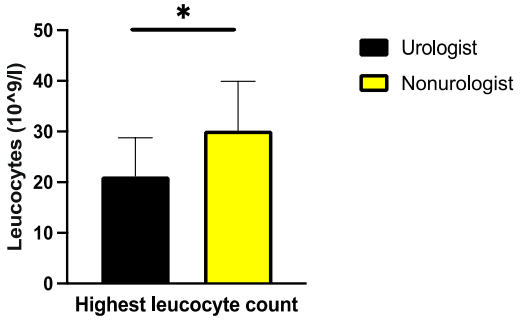

Figure 6. Highest leukocyte count depending on the first medical advice. *Statistically significant.

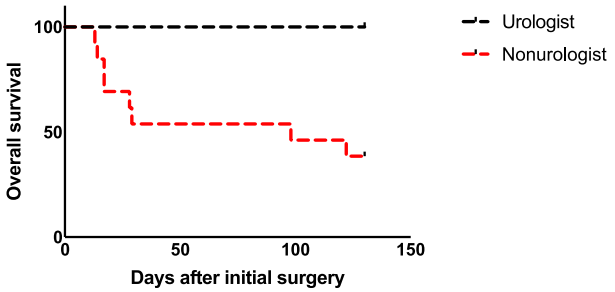

Figure 7. Mortality depending on the first medical advice.

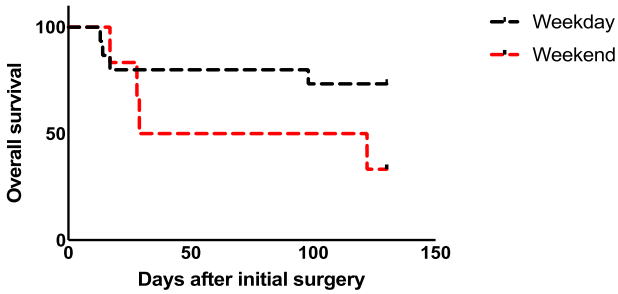

Figure 8. Mortality depending on weekday or weekend admission.

we have seen changes in the levels of procalcitonin, probably not significant because of the small cohort.

The most salient mortality predictor in our cohort was the type of initial consultation, specifically, whether patients were first seen by a urologist or nonurologist. The large difference in mortality between those 2 groups was supported by significant differences in duration of initial debridement as an indirect sign of the extent of the disease, suggesting advanced disease in the group of patients seen by nonurologists. The importance of early specialist consultation is described for several diseases, especially those with a low incidence: In patients with hemophagocytic lymphohistiocytosis, initiation of immunosuppression was significantly earlier after subspecialty consultation.[12] In soft-tissue sarcomas as well, treatment was initiated sooner, if patients were seen by a professional.[13] Furthermore, advantages of a specialist consultation were also found in emergency medicine, where early nephrologist involvement could reduce the risk of renal failure in hospital-acquired acute kidney injury.[14] In patients with *Staphylococcus aureus* bacteremia, infectious disease consultation during acute infection substantially influenced long-term outcomes.[15] Fournier gangrene combines both low incidence and the need for rapid intervention. The specialist consultation in Fournier gangrene is related to the established mortality predictor "transport," which means an admission by an ambulance.[10] A clear line between both risk factors cannot be drawn. From our point of view, however, the importance of initial consultation by a specialist should be brought into focus more—because this variable can be modified in the treatment process of Fournier gangrene. Fournier gangrene still seems to be under-represented in the knowledge of other medical specialties. Therefore, urologists should raise awareness and educate nonspecialists particularly regarding its life-threatening and aggressive course of disease, requiring rapid specialist surgical therapy.

A further focus of this study was to evaluate a potential weekend effect. The weekend effect is mainly described in entities with the need for rapid intervention. A meta-analysis has shown that weekend admission is associated with a significant increase of mortality in patients with nonvariceal upper gastrointestinal hemorrhage.[16] By contrast, a weekend effect could be precluded in entities with a highly standardized protocol of procedures.[17] The duration of initial debridement was significantly longer on the weekend. Nevertheless, there was no significant difference regarding mortality in our cohort, which could be due to the low number of patients enrolled in our study. Apart from that, the fact that there were no statistical differences in the time spans from admission to the hospital and the beginning of initial surgical debridement between weekdays and the weekend confirm the successful application of standard of operating protocols in our university hospital, independent from daytime and weekday, once again emphasizing the importance of standardized protocols and multidisciplinary work in the treatment of Fournier gangrene.

There are some limitations to our study. Mainly because of the small number of patients involved—a

Table 5. *Different Processes Depending on the First Medical Advice*

	Nonurologist	Urologist	*P*-value
Overall survival (median d)	98	130	**.009**[a]
Duration of initial debridement (min)	110 ± 57	55 ± 26	**.019**[b]
Highest leukocyte count (10^9/L)	30.2 ± 9.7	21.2 ± 7.6	**.037**[b]
Lowest hemoglobin (g/dl)	7.8 ± 2.5	8.7 ± 2.4	.468[b]
Days of ventilation (d)	8 ± 7	3 ± 5	.134[b]

[a] Log-rank test.
[b] Student *t*-test.

Table 6. *Different Processes Depending on Weekday Admission*

	Weekday	Weekend	*P*-value
Time span from initial consultation to surgery (min)	449 ± 421	187 ± 91	.152[a]
Operating time of initial debridement (min)	70 ± 37	135 ± 65	**.009**[a]
Highest leukocyte count (10^9/L)	25.8 ± 9	29.3 ± 12.3	.558[a]
Lowest hemoglobin (g/dl)	8.4 ± 2.1	7.7 ± 3.4	.474[a]
Days of ventilation (d)	6 ± 7	7 ± 8	.877[a]

[a] Student *t*-test.

Table 7. *Multivariate Analysis for Predictors of Mortality*

Predictor	*b*	*SE*	CLIB	CLUB	*P*	*OR*
First medical advice	2.815	1.490	0.231	7.779	**.031**	16.693
Highest leukocyte count (10^9/L)	−0.393	0.254	−1.225	0.082	.107	0.675
Lowest hemoglobin (g/dl)	0.038	0.073	−0.180	0.272	.660	1.038
Days of ventilation (d)	0.043	0.080	−0.145	0.313	.631	1.043

95% CILB, lower bound of 95% confidence interval of regression coefficient; *b*, estimated regression coefficient; CIUB, upper bound of 95% confidence interval of regression coefficient; *OR*, odds ratio; *P*, *P*-value of the test that regression coefficient = 0; *SE*, standard error of regression coefficient.

consequence of the low incidence of the disease—and its retrospective study, it remains debatable whether our conclusions drawn in one single German center regarding the initial consultation are transferrable nationwide or globally. Thus, our findings need to be approved by larger cohort studies and need to be compared with other health care systems, particularly those in nonindustrial countries. A retrospective multicenter study including most university hospitals in German is on its way.

CONCLUSION

Despite the small cohort, we were able to show a significant correlation between the specialization of the doctor in the initial clinical consultation, either a urologist or nonurologist, and the patient's mortality with lower mortality when patients are first seen by a trained urologist. Considering the life-threatening potential of Fournier gangrene, professionals should develop strategies to educate nonurologists and raise awareness about this disease and its clinical presentation to optimize rapid intervention and reduce mortality.

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