

**Location of residence and mortality for patients diagnosed with Fournier's gangrene**

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**Abstract**

**Introduction:** Fournier's gangrene (FG) is a necrotizing infection of the genitalia. Time from to surgical intervention is a critical determinant of prognosis. We sought to investigate whether patients from rural locations have worse clinical outcomes given distance from a tertiary center.

**Methods:** The Manitoba Intensive Care Unit (ICU) registry includes patients who have been admitted into ICUs across Manitoba. We identified patients admitted with FG from February 1999 to October 2019. Age, gender, Charlson comorbidity index (CCI), presence of colostomy and scrotal debridement, length of stay (LOS), and mortality outcomes were obtained. Patients were categorized as being rural or urban.

**Results:** From 1999–2019, a total of 79 patients were admitted with FG. The median age was 60 years [interquartile range [IQR] 48–67). The mortality rate during hospitalization was 16.5%. There was no statistically significant difference in the number of deaths for patients from urban vs. rural dwellings (9/47 [19.1%] vs. 4/32 [12.5%],  $p=0.434$ ). A comparison of the 66 (83.5%) patients that survived and the 13 (16.5%) that died during ICU hospitalization demonstrated no difference in age, gender, CCI, presence of colostomy, and rates of scrotal re-debridement ( $p>0.05$ ). Multivariable analysis demonstrated that living in a rural area was not associated with increased mortality (odds ratio 0.64, 95% confidence interval 0.16–2.57,  $p=0.527$ ).

**Conclusions:** Location of residence was not predictive of death from FG. In addition, baseline characteristics such as age, gender, CCI, surgical interventions, or LOS were not found to be associated with mortality.

## Introduction

Fournier's gangrene is a necrotizing soft tissue infection that begins in the subcutaneous tissues which can progress rapidly and may lead to disseminated intravascular thrombosis and subsequent necrosis.<sup>1</sup> Despite advancements in medical technology, mortality rates remain high at 3.5% - 45%.<sup>2,3</sup> Although multiple factors influence mortality, early surgical intervention appears to be the most important factor with the greatest impact on clinical outcomes, followed by antibiotics and adequate resuscitation.<sup>3,4,5,6</sup> Late presentation to a treatment center causes extensive anatomical and physiological damage in patients, leading to poor outcomes.<sup>7</sup> Multiple studies examining optimal time for surgical intervention in FG have reported a range of numbers including 7 days from onset of symptoms, to 2 days from time of admission.<sup>8,9</sup> Despite the lack of consensus on exact timing, the principle of early surgical intervention remains consistent.

Necrotizing infections such as FG are the most severe class of skin and soft tissue infections (Class IV), defined as being life threatening and often requiring admission to an Intensive Care Unit (ICU).<sup>10</sup> Studies involving FG reveal that approximately 10% of FG patients require mechanical ventilation and 1.4% need dialysis. Most rural hospitals lack these resources and must urgently transfer these patients to tertiary care centers. A 2011 Canadian census found that 18.9% of Canadians lived in rural areas away from tertiary care centers.<sup>11</sup> One study demonstrated that patients presenting to care centers via transfer had an increased risk of death.<sup>12</sup> While other studies show that rural patients who require interhospital transfers for treatment of sepsis have higher rates of mortality.<sup>13</sup> This may potentially be due to delays from diagnosis to the time of definitive management as a result of transport time between hospitals.<sup>14</sup> To our knowledge, there have been no studies examining FG outcomes based on rurality.

In this study, we evaluate the impact of living in rural dwellings on mortality from FG, compared to those living in urban centers.

## Methods

The Manitoba ICU database was initiated in 1999 and currently contains data on 140,777 patients who have been admitted into ICUs across Manitoba. We identified patients admitted to the ICU with a diagnosis of FG from February 1999 to October 2019 (Figure 1), patients before 2019 were identified using a local code, and patients after 2019 were identified using ICD 10 code 49.3. Only patients with a record of their residence were included for the analysis. They were categorized into rural and urban groups using the first two digits of their postal code for their primary address which we correlated against the established postal code system. All patient that were admitted to the ICU underwent urgent surgical debridement at time of admission. Patient demographics including age, gender, and Charlson comorbidity index (CCI) were recorded. Outcomes including need for colostomy, scrotal re-debridement, length of stay in the ICU (LOS) and mortality were obtained with the primary outcome of interest being in hospital mortality between our urban vs rural population.

Statistical analysis was performed with SPSS version 24 (Chicago, USA) software. Analysis was performed per patient, for patients with multiple ICU admission related to FG, readmission was analyzed as a dichotomous variable, LOS in the ICU was obtained by adding all the days for the admission in the ICU, and for analysis purpose the CCI on first admission was considered for the statistical analysis standpoint. For continuous variables medians with interquartile ranges [25-75] were reported based on data distribution, and comparison between groups was performed using the U Mann-Whitney test. Categorical variables were presented as absolute values and frequencies and analyzed with a Chi-square or Fisher's exact test as required. A multivariable-adjusted logistic regression analysis was performed to calculate the risk of death in accordance with the clinical and demographic characteristics of the patients. A p-value < 0.05 was considered statistically significant.

## Results

A total 79 patients over the 20-year study period, overall patients had a total of 94 admissions to the ICU, 69 patients had a single admission to the ICU and 10 had FG related readmissions to the ICU (6 had 1 readmission, 3 had 2 readmissions, and 1 had 3 readmissions). Median patient age was 60 [48 – 67] years, with the majority of patients being male, n = 65 (82.3%). With respect to location of residence, 47 (59.5%) admissions were from residents living in urban areas, and 32 (40.5%) for those residing in rural regions. Comparisons between the clinical and demographics characteristics between groups are presented in Table 1.

The mortality rate for patients admitted to ICU with FG was 13 (16.5%). There was no statistically significant difference in the number of deaths for patients from urban vs. rural dwellings [9/47 (19.1%) vs. 4/32 (12.5%); p=0.434] (Figure 1).

The morbidity rate for patients from urban vs. rural settings were also analyzed. There were no significant difference in presence of a colostomy [4/47 (8.5%) vs. 4/32 (12.5%); p=0.708] or scrotal re-debridement [8/47 (17%) vs. 8/32 (25%); p=0.386] between these two groups (Figure 1).

Demographic and clinical outcome variables were analyzed based on survival status (Table 2). No significant differences were noted including age, gender, CCI, rurality, or LOS between the 66 (83.5%) patients that survived and the 13 (16.5%) deaths (p > 0.05).

A multivariable-adjusted logistic regression analysis demonstrated that age, sex, history of ICU readmission, scrotal re-debridement, CCI, or LOS were not significantly associated with mortality (p > 0.05) (Table 3). Additionally, living in a rural area was not associated with mortality OR = 0.64 (CI 95%: 0.16 - 2.57; p = 0.527).

## Discussion

In our cohort of patients who were admitted to Manitoba ICUs for FG, we found that baseline factors such as age, gender, CCI, surgical intervention (colostomy and scrotal debridement),

LOS, readmission nor rurality were predictive of mortality. Moreover, there was also no difference in the need for a colostomy, scrotal debridement or length of stay – which are factors indicating potential severity of infection on initial presentation. This however should be understood also in the context of the number of patients involved. Although there was no statistical difference, 8/66 (12.1%) patients who survived received colostomy vs 0/13 (0%) in the group that died. When looking at scrotal re-debridement, 15/66 (22.7%) patients who survived underwent this procedure versus only 1/13 (7.7%) of patients who died. This is interesting as in those patients who received more intensive surgical management, Korkut et al, reported mortality amongst patients was increased.<sup>8</sup> The results of our data may reflect the need for larger number of cases for us to infer any conclusive statement, or it may indicate that more aggressive surgical management, despite what is previously reported, may be helpful in improving mortality rates rather than the theory that extensive surgical intervention is secondary to worse clinical presentation thereby leading to poorer mortality outcomes. Chen et al, supports this theory showing that patients receiving a primary diverting colostomy had mortality rates of 16.7% vs patients who received a secondary diverting colostomy having mortality rates of 40%.<sup>15</sup> Another possibility is that this procedure was recommended more for cases who were thought to have a better post-operative prognosis, and patients who had a more severe clinical presentation may have been placed on a palliative course of care and therefore did not undergo scrotal re-debridement despite qualifying for it clinically. Co-morbidities as a significant risk factor for poor FG outcomes have also been well described in the literature, with rural populations often suffering a greater health burden than their urban counterparts.<sup>16</sup> Although no specific studies have looked at our population diagnosed with FG, our findings, despite a small number of total cases, show no difference between rural vs urban populations when their co-morbidities were measured using the CCI. This allows us to interpret our results without the confounding element of co-morbidities, knowing that this is a significant factor influencing mortality in patients with FG.<sup>17</sup>

Time to surgical management of FG is a critical determining factor of mortality, however optimal timing continues to be debated.<sup>18</sup> Surgical debridement within 14.35 hours can reduce mortality by 45% in high risk patients.<sup>3</sup> However, one study demonstrated diagnostic delays up to 12 days due to non-specific complaints and masked presentations, such as simple cutaneous infections, urinary tract infections, and constitutional symptoms.<sup>19</sup> Despite the rapidly progressive infection associated with FG, opportunities for earlier diagnosis and prompt surgical intervention may potentially exist in the non-specific stage of infection. Despite presumed delays in presentation due to greater transport times from rural areas to tertiary care centers, our analysis demonstrated no differences in mortality. This may reflect efficient interfacility transfers and effective protocols in place at the provincial level. It may also suggest that the lengthy prodrome period allows for a negligible difference in transport time depending on the severity of the infection at the time the patient seeks medical attention. Another possibility is that in addition to

prodrome period, once the patient has reached what would medically be classified as FG, there remains an adequate window of time before the mortality threshold is reached. These results may also be due to multifactorial nature of this disease. Antibiotics and other forms of medical resuscitation which do not hold the same time constraints as surgical time and can be started prior to transport to a tertiary center may also play a significant role in reducing the impact of delayed operative treatment. In fact, multiple studies have suggested that IV antibiotics should be initiated within the first hour following recognition of sepsis or septic shock and increasing delays in time to administration were directly correlated with increase in mortality.<sup>17,20</sup> More interestingly however, is that while time to surgical debridement may be generous in its window of time, we expect that extent of tissue involvement is in direct correlation with time, yet there was also no difference between our rural vs urban populations in need for colostomy or length of stay required for prolonged healing times with more aggressive debridement. Our overall mortality rate was 16.5%, which on the lower end of the quoted 10-50%, with rates as high as 88% shown in other studies.<sup>2,21</sup> This may also signify that despite our data showing no statistical difference, our population may not have been large enough or sick enough for us to confer any conclusive meaning.

The present study has several notable limitations due to the retrospective nature of our analysis. Firstly, the patients were stratified according to rural vs urban based on postal code, however we were unable to stratify the analysis based on distance to tertiary centers. In addition, patients may have registered with a rural address, but were in an urban setting at the time of symptom onset. Secondly, time to surgical intervention was not captured in our database and therefore our analysis could not be controlled for unanticipated factors delaying surgery further. Thirdly, other clinical markers of disease severity, which are known predictors of worse outcomes, were not captured in this database and could not be used to adjust for the FG Severity Index.<sup>21</sup> Lastly, in order to identify patients for our study, we utilized a local ICU code for patient prior to 2019, and ICD-10 codes thereafter. This is dependent on patients being currently identified, which may have an element of error.

### Conclusions

Critically ill patients admitted to ICU with FG had a 16.5% in hospital mortality. Rurality did not significantly increase the risk of mortality from FG. Further studies examining the timing of transport and time to operative management for rural patients are needed to optimize care and outcomes from FG.

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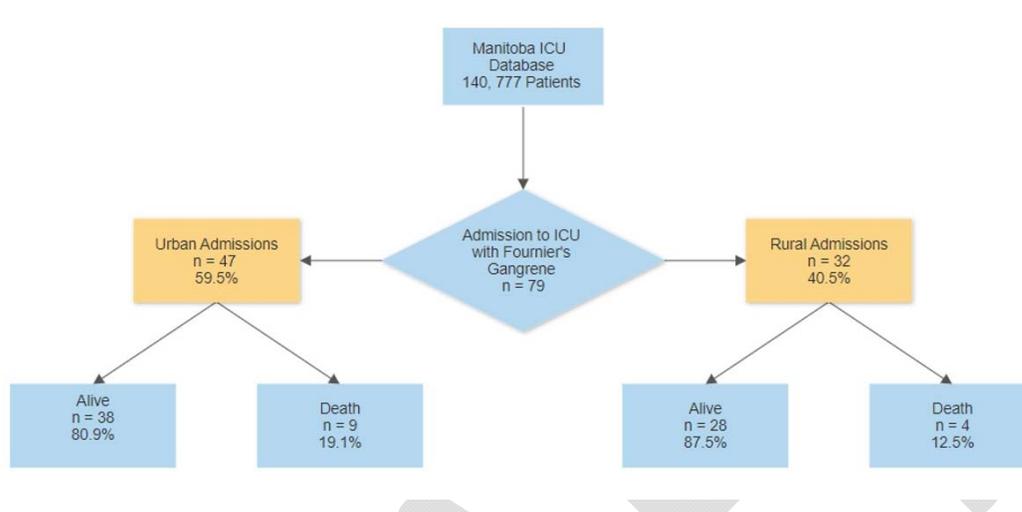
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## Figures and Tables

Fig. 1. Flowchart of inclusion and hospital mortality stratified by location of residency.



Variable	Overall n=79 (100%)	Urban n=47 (59.5%)	Rural n=32 (40.5%)	p
Age in years	60 (48–67)	60 (49–69)	59.5 (46.5–66)	0.708
Sex				
Male	65 (82.3%)	40 (85.1%)	25 (78.1%)	
Female	14 (17.7%)	7 (14.9%)	7 (21.9%)	0.550
CCI	2 (1–4)	2 (1–4)	2 (1–4.8)	0.719
Readmission				
No	69 (87.3%)	40 (85.1%)	29 (90.6%)	
Yes	10 (12.7%)	7 (14.9%)	3 (9.4%)	0.732
Colostomy				
No	71 (89.9%)	43 (91.5%)	28 (87.5%)	
Yes	8 (10.1%)	4 (8.5%)	4 (12.5%)	0.708
Scrotal re-debridement				
No	62 (78.5%)	39 (83%)	24 (75%)	
Yes	17 (21.5%)	8 (17%)	8 (25%)	0.386
LOS (days)	5 (2.3–13)	3.8 (1.7–13)	6.1 (3.5–13.6)	0.205
Mortality				
Alive	66 (83.5%)	38 (80.9%)	28 (87.5%)	
Death	13 (16.5%)	9 (19.1%)	4 (12.5%)	0.434

Values are n (%) or median (interquartile range [IQR] 25–75); CCI: Charlson comorbidity Index; LOS: length of stay.

Variable	Survived n=66 (83.5%)	Deceased n=13 (16.5%)	p
Age in years	58.5 (46–66.3)	66 (51–72.5)	0.195
Sex			
Male	53 (80.3%)	12 (92.3%)	
Female	13 (19.7%)	1 (7.7%)	0.444
Location			
Urban	38 (57.6%)	9 (69.2%)	
Rural	28 (42.4%)	4 (30.8%)	0.434
CCI	2 (1–4)	4 (1.5–5)	0.105
Readmission			
No	59 (89.4%)	10 (76.9%)	
Yes	7 (10.6%)	3 (23.1%)	0.355
Colostomy			
No	58 (87.9%)	13 (100%)	
Yes	8 (12.1%)	0	0.340
Scrotal re-debridement			
No	51 (77.3%)	12 (92.3%)	
Yes	15 (22.7%)	1 (7.7%)	0.286
LOS	4.7 (2.1–11)	8.3 (3.4–24.8)	0.105

Values are n (%) and median interquartile range [IQR] 25–75; CCI: Charlson comorbidity index; LOS: length of stay.

Variable	OR	95% CI	p
Age (years)	1.02	0.97–1.07	0.388
Sex			
Male	1		
Female	0.19	0.02–2.02	0.168
CCI	1.26	0.95–1.68	0.110
Readmission			
No	1		
Yes	1.98	0.36–10.96	0.435
Location			
Urban	1		
Rural	0.64	0.16–2.57	0.527
Scrotal re-debridement			
No	1		

**Link between location of residence and mortality in Fournier’s gangrene**

Yes	0.25	0.03–2.29	0.218
LOS (days)	1.01	0.98–1.04	0.391

CCI: Charlson comorbidity index; LOS: length of stay.

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