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Project Title: Physical health outcomes in necrotizing fasciitis patients: A population-based, longitudinal administrative study

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Summary (250 words max single spaced):

Necrotizing fasciitis (NF) is an acute, rapidly spreading, infection of the fascia associated with extensive surgery, amputations and prolonged hospitalization. Previous studies have shown that NF is also associated with a high degree of comorbidity. It is not clear if NF results in an increased rate of negative physical health outcomes (PHOs) in NF patients in the years after the injury compared to the pre-existing high rate before the occurrence of NF. We examined a longitudinal population-based sample of 167 NF cases compared to 835 controls (matched 1:5 based on age, sex and physical aggregated diagnostic groups) regarding PHOs by linking patient data from the NF registry with administrative data at the Manitoba Center for Health Policy. We examined for one or more of the following PHOs: arthritis, coronary artery disease (CAD), diabetes, hypertension, fractures or total respiratory morbidity (TRM). No significant change was found in the adjusted relative rate of PHOs in the post NF index date time period compared to 2 years pre NF in cases compared to matches. The high mortality rate in the post NF index date time period posed a risk for introducing a lead time bias and therefore a subset analysis of 111 survivors and 525 associated surviving matches was conducted. In this subpopulation, a significant increase in the ARR of any PHO was found. Therefore, we found evidence to suggest an increase in the ARR of physical health outcomes in the years following a bout of NF compared to the years prior.

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Author: Kevin Shek

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Introduction

Necrotizing fasciitis (NF) is an acute, rapidly spreading, infection of the fascia [1]. Progression of NF quickly leads to systemic toxicity and, if not treated expediently, death. Treatment includes early surgical debridement, infection control, fluid and nutritional support, and eventually wound coverage, usually via skin grafting. The extensive surgeries, amputations and prolonged hospital stay, often requiring ICU admission, that result from treatment are known to put additional stress on patients and may have deleterious long term consequences.

It is known that patients with similar types of injuries, such as burn survivors, have an increased relative rate of physical health outcomes (e.g. arthritis and hypertension) compared to age and sex matched controls [2]. NF is more severe than burns in that NF patients: have greater hospital LOS even when normalized for %TBSA, are more likely to spend time in the ICU, receive more blood transfusions, and require more procedures and amputations [3]. Therefore it is conceivable that NF survivors will also have increased rates of adverse physical health outcomes in the years following their infection.

Light et al have shown [4] that NF patients who survive to discharge have a significantly higher mortality rate compared to standardized rates (age and sex) in the general population. For example, someone who had NF at age 50 and survived to discharge had a decrease in life expectancy by 20-25 years. This high long term mortality rate may be related to increased rates of physical health outcomes resulting from NF and its associated treatment in hospital. However, Light et al [4] did not take into consideration that NF patients already have a high rate of preexisting comorbidities that may predispose them to an increased mortality rate regardless of the presence of NF. Therefore, it is not actually known what the effect of NF and its associated treatment is on the rate of post NF physical health outcomes in the context of the high rates of preexisting morbidity. Better understanding of long-term physical health outcomes will help guide patient care by improving the physician's ability to predict patients at high risk of adverse physical events after NF hospital admission and allow implementation of guided long term follow up.

The following study was undertaken in order to test the hypothesis that survival from NF and its treatment will lead to an increased relative rate of physical health outcomes after the NF infection compared to before the NF infection. A NF survivor cohort was derived from a prospectively collected population based registry with controls identified from the general population who were matched on age, sex and number of physical aggregate diagnostic groups (PADGs). PADGs are calculated using the Adjusted Clinical Group (ACG) system, which assigns individuals to 1 of 32 major PADG groups based on utilization of physician and hospital services throughout the previous year. The number of PADG groups to which an individual qualifies is an indication of the impact of their level of comorbidity. The unadjusted relative rate (URR) of physical health outcomes in NF cases and matches was calculated comparing the rate for 2 years before the NF date to the rate after the NF date. The date of hospitalization for NF has been termed the 'index' date for comparison with the control population. Physical health outcomes that were measured include arthritis, coronary artery disease (CAD), diabetes, hypertension, fractures, total respiratory morbidity (TRM), and any physical health outcome.

These diagnoses were chosen as they have been previously identified as clinically important diagnoses whose identification using this data has been validated. Matches were assigned the same index date as their respective case. The URR of physical health outcomes between groups over these two time periods (pre and post) was calculated, adjusting for covariates (sex, urban vs rural, rich vs poor) to determine if there is a significant change in the adjusted relative rate (ARR) of physical health outcomes for the NF group compared to matched controls over the study period. The pre period includes 2 years prior to the NF index date, while the post period includes all follow up post NF index date up to March 31, 2015. This extended post NF index date time period was chosen to capture the maximum possible number of outcomes.

Methods

Setting

The study protocol was reviewed and approved by the University of Manitoba ethics review board, and Manitoba Health Information Privacy Committee (HIPC).

Study Design

This study is a population based, matched (1:5) cohort study using clinical data linked to longitudinal administrative data housed at the Population Health Research Data Repository located at the Manitoba Centre for Health Policy (MCHP).

Data Sources

Data for this study were obtained from the Population Health Research Data Repository located at the MCHP at the University of Manitoba in Winnipeg, Manitoba, Canada. This data set includes de-identified, individual-level data for the entire population of Manitoba (1.3 million) from 1984 onwards. The population receives healthcare through a provincially administered insurance program with all physician and hospital billing being paid through a personally unique provincial health information number (PHIN). Patient information can be linked between the MCHP data sets through a scrambled PHIN to create a longitudinal record of health care interactions and utilization. This methodology was employed to access anonymized subject data for individuals found in the regional NF Registry. The NF Registry is a dataset containing clinical information on all patients with NF who sought care at the province's three tertiary care centers. All patients with information in the registry have NF confirmed by documentation of fascial involvement at the time of surgery. This cohort does not include necrotizing soft tissue infections that do not involve the fascia. The Canadian health system changed over from ICD-9-CA to ICD-10-CM in 2005.

Study Population

The study investigated outcomes in 2 groups: (1) individuals who were admitted for NF and survived to discharge from hospital as cases (n=167) and (2) a matched cohort drawn from the general population (assigned the same index date as the matched NF individual) (n=835). The NF cohort was identified from the NF Registry. This study contains patients ≥ 17 years old, who survived to discharge from the Health Sciences Centre, St. Boniface Hospital or Brandon General Hospital between April 30, 2004 – March 30, 2013 with a diagnosis of NF. Individuals from outside of Manitoba were excluded as they could not be linked to the MCHP database. Previous work by our group [5] has shown that all NF survivors are treated at one of these three sites in Manitoba, making this registry inclusive of population level data. ICD-9-CA codes used were: NF (M72.6), Fournier's Gangrene (male/female: N49.3/N76.8), and myositis (M60). The patient charts were reviewed and confirmed as a true NF case based on macroscopic confirmation at the time of surgical debridement.

Matching was based on NF case age at the index date, sex, location of residence (regional

health authority, based on the postal code), and PADG grouping (0, 1-2, 3-5, 6+). Matching based on the specific number of PADGs resulted in only 85% success, whereas matching using PADG grouping resulted in 100%, so the grouping of PADGs was used in the study.

Time Frame

January 1, 2004 was the earliest possible index date in the study and March 31, 2013 the latest possible. Cohorts were compared for physical health outcomes two years prior to the index date ("Pre") and the rate either at the end of the study, March 31, 2015, or until they passed away ("Post").

Outcomes

Coding for physical health outcomes of interest include: arthritis (includes rheumatoid arthritis, osteoarthritis, connective tissue disorders, ankylosing spondylitis, or gout; ICD-9-CA: 274, 446, 711, 721, 725-729, 739; ICD-10-CM: M00-M05, M05-M07, M10-19, M30-36, M65-M79), cancer (ICD-9-CA: 140-208; ICD-10-CM: C000-C419, C450-C97), coronary artery disease (ICD-9-CA: 401-414; ICD-10-CM: I20-I25), diabetes (ICD-9-CA: 250; ICD-10-CM: E10-E14), fractures (ICD-9-CA: E800-E879 and E890-E999 or ICD-10-CM: V01-V99), hypertension (ICD-9-CA: 401-405; ICD-10-CM: I10-I13, I15), total respiratory morbidity (includes asthma, chronic or acute bronchitis, emphysema, or chronic airway obstruction and chronic obstructive pulmonary disease; ICD-9-CA: 466, 490-493 or 496 or ICD-10-CM: J20, J21 or J40-J45). Any physical outcome included individuals with any one or more of the aforementioned outcomes. Outcomes were based on validated diagnostic definitions for the Manitoban population [6,7].

Statistical Analysis

Descriptive statistics are shown as a proportion (%) or mean \pm std. dev. (range). The first set of analyses calculated the crude unadjusted relative rates (URRs) for the outcomes of interest in NF cases relative to matches in the 2 year period before the index date and the period of time following NF. The second set of analyses compared the NF cases relative to the matches using adjusted relative rates (ARRs) for each outcome in generalized estimating equation (GEE) regression assuming a Poisson distribution. GEE models were used to account for correlated observations. We adjusted for the following covariates: sex, income and location of residence. Income was based on income quintiles with the lowest 2 quintiles and income "not found" termed "poor". Location of residence was a binary variable based on whether they lived in urban or rural setting. A "period \times group" interaction term was included in the model which allowed comparison of the change in RR of outcomes between the two groups before and after the NF index date.

Results

The 167 NF cases and 835 matches were found to both have a median age of 49.7 years old and each cohort was comprised 49.7% of men (**Table 1**). There was no significant difference between cases and matches with regards to age, distribution of sex, location of residence (urban vs rural), or PADG grouping which demonstrates that matching was successful. We found that a significantly greater proportion of poor individuals comprised the cases compared to matches ($p < 0.001$). Thus, we decided to use income as a co-variate in subsequent analysis due to its possible role in physical health outcomes. As well, an examination of the PADG groupings showed that a PADG score range of 6+ was the most common (45.5%), indicating that there is a high rate of pre-existing co-morbidity in these groups.

A comparison of the unadjusted relative rates (URR) of physical health outcomes in the post NF index date time period for cases and matches is shown in **Table 2**. Cases have a significantly higher ($p < 0.05$) URR for arthritis, CAD, diabetes and any physical health outcome relative to

matches.

We then examined the relative rates adjusted for sex, income and location of residence (ARRs) of physical health outcomes in 167 NF cases and 835 matches for the post NF index date time period (**Table 3**). A generalized estimating equation (GEE) was used. The post NF index date ARR was significantly increased in cases compared to matches for arthritis, CAD, diabetes, and any physical health outcome ($p < 0.05$). However, since it is known that NF patients are a highly comorbid population even before their NF infection, we calculated the 2 years pre NF ARR of physical health outcomes. Cases already had a significantly greater ARR of arthritis, diabetes, fractures, and any physical health outcome compared to matches in the 2 year pre NF time period showing that despite being matched for PADG they had preexisting higher rates of physical health outcome before developing NF. A pre-post "period \times group" interaction term was used to determine if there was a change in the ARR in cases compared to matches in the post NF index date time period compared to the 2 year pre NF time period (i.e. Was there a change in the relative rates over time?). Counter intuitively the ARR of diabetes, TRM and any physical health outcome were found to be decreased in the post index date part of the study compared to the pre index date rates in the NF group.

Analysis of mortality found that a significant proportion of the NF cases died in the examination time period; 56/167 cases (33.5%) died compared to only 30/835 (3.6%) in the matches (**Figure 1**). Only 111 NF patients survived the entire follow up period to March 31, 2015. **Table 4** shows the comparison of characteristics between surviving and deceased NF cases. The mean age was significantly lower in surviving NF cases (45.6 ± 15.8 yr) compared to deceased cases (57.7 ± 12.2 yr, $p < 0.001$). NF cases who passed away also trended towards a higher mean PADG (5.8 ± 3.2) compared to surviving NF cases (4.9 ± 3.2 , $p = 0.08$). Surviving NF cases were significantly less likely to require ICU stay and as expected also had a significantly longer length of follow up than deceased cases (6.1 ± 2.2 vs. 2.1 ± 2.4 years, respectively, $p < 0.001$). There was no difference in the number of surgical procedures or likelihood of receiving an amputation.

We found 44.6% of the deceased cases died within the first 12 months after NF index date (**Figure 2**). Given the high and fairly rapid post index date death in the NF group we performed a subset analysis on NF cases and associated matches that survived the entire study period. We excluded the 56 NF cases who died before the end of the follow up period, and their 280 associated matches (**Figure 1**). These reflected patients who did not have 'significant time at risk'. Thirty more matches associated with surviving NF cases were removed because they passed away during the course of the study. The cases associated with the deceased matches were still included because these cases still had other matches minimizing the effect of eliminating the data from these matches. Furthermore, the 1:5 matching ratio is a pragmatic ratio. Having a ratio of slightly less than 1:5 for NF 30 cases was not felt to have a significant impact on the results. This resulted in 111 cases and 525 matches.

We analyzed the URR of physical health outcomes in NF surviving cases compared to matches for the post NF index date time period (**Table 5a**) Similar to the prior analysis on 167 NF cases and 835 matches there were significant increases in the URR of arthritis, coronary artery disease (CAD), diabetes, fractures and any physical outcome among surviving NF cases compared to matches ($p < 0.05$).

To explore the potential that the higher post NF index date rates reflect preexisting comorbidity, we then examined the pre index date rates, conducted in a similar way to the prior analysis 167 NF cases and 835 matches shown in **Table 2**. **Table 5b** shows the physical health outcomes of

NF cases and matches in the 2 years before the NF index date. There were significantly higher URRs of arthritis, diabetes, fractures, and any physical health outcome among cases compared to matches ($p < 0.05$). These data show that the subset population of surviving NF cases also have a high rate of pre-existing chronic co-morbidities before their bout of NF.

In order to examine the change in ARR of physical health outcomes in surviving NF cases and matches, we used GEE, adjusting for location of residence, income, and sex. **Table 6** shows the post index date ARR of physical health outcomes for NF cases compared with matches to the 2 year pre index date adjusted relative rates. This showed that while no single outcome was significantly changed over time, the ARR for any physical outcome significantly increased ($p = 0.039$).

Discussion

There is a plethora of literature on the acute presentation of NF, the high preexisting comorbidity associated with these patients and the associated hospital treatment. Light et al [4] showed an increase in the long term mortality rate in NF patients in the years following their hospital discharge compared to the general population. However, little has been reported on long term changes in rates of physical health outcomes for this patient population. The study we are presenting, to our knowledge, is the first to look at the rate of physical health outcomes in the years following NF. Our unique study design of matching on comorbidity and comparing pre NF to post NF relative rates between cases and matches allows us to show a difference in the ARR of physical health outcomes in the post NF compared to pre NF time period in cases compared to matches, accounting for the high preexisting rates of comorbidity in the NF population.

Initial analysis of the 167 NF cases and 835 matches found a significant decrease in the ARR for diabetes, TRM and any physical health outcome in cases compared to matches over the study period. This seemed counterintuitive because we hypothesized that NF and its associated treatment would have a deleterious effect on physical health outcomes, whereas these results showed an apparent protective effect.

Mortality analysis showed that 56/167 (33.5%) of the NF cases died in the post index date period, compared to 30/835 (3.6%) in the matches. Furthermore, over 40% of deaths in the NF cases occurred within the first year post hospital discharge. By comparing the surviving 111 NF cases to the 56 deceased NF cases, we showed that the deceased NF cases were a sicker group of individuals (e. g. more likely to be in ICU, longer ICU stay, trending towards more ADGs).

There is significant potential for the introduction of a lead time bias with 33.5% of NF cases passing away in the early post NF time period. Many of these NF cases, due to their rapid death, had a short time period to demonstrate physical health outcomes compared to those who survived the duration of the study period. This made the rates in the post NF index date time period appear to decrease.

The subset analysis on the 111 surviving NF cases and 525 matches was then performed to take into account the potential for lead time bias effecting the results. Even then, however, only any physical health outcomes showed a significant increase in the ARR in cases compared to matches for the post NF index date time period compared to the 2 years pre NF index date. None of the specific physical health outcomes showed a similar increase. We postulate that this could be the result of not having enough power to show the increase for specific physical health outcomes (type I error).

NF survivors were still a relatively unhealthy population in the post NF time period due to their rates of comorbidity before developing NF. For example, 95.5% had arthritis, 41.4% had diabetes, and 46.0% had hypertension in the post NF index date time period. In comparison, a 2013 report stated that only 19% of Manitoban adults self reported having arthritis on Canadian Health Surveys [8]. The Canadian Diabetes Association reported that 7.6% of the general Manitoba population had diabetes in 2010 [9]. Finally, the Manitoba government reported that 27.2% of Manitobans older than 20 had hypertension in 2009/10 [10]. Therefore, these high rates of physical health outcomes in NF survivors compared to the general population warrant attention from healthcare professionals.

We demonstrated a possible relationship between comorbidities on mortality compared to an age standardized population rate published by the Government of Canada. The mortality rate in the matches was elevated at 3.6%, however the mortality in NF cases of 33.5% is especially concerning. The mortality rate for Manitobans of similar age (55-59 years old) has been shown to be 0.59% [11]. Hence the NF survivors in our population have a 57 times greater mortality rate than the general population. Furthermore, post discharge mortality rate appears to be greater in our population than the 25% mortality reported by Light et al in NF [4] patients from their institution who had a mean follow up period of 3.3 years. However, Light et al excluded patients who died within 30 days of hospital discharge, a time period which may be associated with a high rate of mortality. The results of our study therefore indicate that NF survivors are at increased risk for premature mortality and further studies are needed to better understand the cause and identify possible interventions.

Limitations

Our study should be interpreted within its limitations. First, we cannot account for individuals who do not or are unable to seek medical care, since administrative data relies on physician claims and hospital abstract data. Second, in physician billing, only one ICD code is reported which may result in underreporting of physical health outcomes in those with multiple medical issues. However, we believe that any possible treatment seeking and/or reporting bias is likely equal in both cases and matches. Third, our use of an extended post NF index date time period for follow up may have resulted in a convergence of the rates between cases and matches. This is likely due to both groups trending towards similar rates of physical health outcomes as time progresses from the NF index date, especially in this aging population. Finally, we defined physical health outcomes based on ICD codes that were submitted through physician claims and hospital abstracts. While not diagnostic for these diseases, the use of these codes to identify resource use changes over time and between groups has been validated and is a good indicator of relative differences in these outcomes.

Strengths

First, this is a population-based study of NF patients in Manitoba with a large matched cohort making these results more generalizable. Second, we used previously validated algorithms for defining the physical health outcomes. Third, the ability to match based on degree of comorbidity was instrumental in identifying if the changes in post NF outcomes were a result of the NF and its associated treatment or the presence of comorbidities. Fourth, our ability to compare pre index to post index rates of the outcomes reduced the effect from these preexisting outcomes. Finally, we identified a high mortality rate in NF cases following hospital discharge, leading us to conduct a subgroup analysis on only those that survived the full time of follow up. Future studies assessing long term consequences of NF should take into account the potential reduction in perceived differences due to this high mortality rate.

Conclusion

NF patients often have a complicated medical history that appears to be worsened after NF infection and its treatment. Post discharge, these patients are not only at greater risk of adverse physical health outcomes, they are at nearly a ten times greater risk to die than matched controls with similar comorbidities and have an over 50 times greater mortality rate than the 'average' Manitoban of a similar age. Thus, it is important to closely follow up NF patients after discharge and for an extended period of time.

Appendix

The measure of comorbidity that was utilized in the matching process was number of physical aggregated diagnosis groups (PADGs) of the ACG classification system [12]. Medical providers indicate diagnoses using International Classification of Disease codes (ICD-9 or ICD-10 codes depending on the year). The ACG software groups ICD codes into 32 ADGs on the basis of: 1) duration of the condition, 2) severity of the condition, 3) diagnostic certainty, 4) etiology of the condition, and 5) specialty care involved. Individuals are assigned an ADG if they have been diagnosed with any of the ICD codes in the group in either an outpatient or hospital visit over the past year. Patients can be assigned from 0 to 32 ADGs and then grouped into 0, 1-2, 3-5, and 6+ ADG groups to quantify the degree of their comorbidity and expected health resource utilization.

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Figure and Tables

Table 1: Descriptive characteristics of the NF cases and matches

	Case (n=167)	Match (n=835)	P
Age	49.7 ± 15.7 (17-89)	49.7 ± 15.7 (17-89)	N/A
Gender (male)	83 (49.7%)	415 (49.7%)	N/A
Urban (%)	85 (54.1%)	443 (56.4%)	N/A
Poor (%)	98 (62.4%)	330 (42.0%)	<0.001
PADG score			
0	6 (3.6%)	30 (3.6%)	N/A
1-2	34 (20.4%)	170 (20.4%)	N/A
3-5	51 (30.5%)	255 (30.5%)	N/A
6+	76 (45.5%)	380(45.5%)	N/A

*Urban vs rural: n=157 cases, n=786 matches

*Rich vs poor: n=157 cases, n=786 matches

Note: PADG, physical aggregated diagnosis groups

Table 2: Rates of physical health outcomes of cases compared with matches, in the years following the NF index date

Outcome	Case (n=167)	Match (n=835)	URR (C.I. 95%)
Arthritis	156 (93.4%)	563 (67.4%)	6.85 (3.66-12.84) ¹
Cancer	26 (15.6%)	124 (14.9%)	1.06 (0.67-1.67)
CAD	35 (21.0%)	110 (13.2%)	1.75 (1.14-2.67) ¹
Diabetes	66 (39.5%)	220 (26.4%)	1.83 (1.29-2.58) ¹
Fractures	36 (21.6%)	133 (15.9%)	1.45 (0.96-2.19)
HTN	73 (43.7%)	392 (47.0%)	0.88 (0.63-1.23)
TRM	55 (32.9%)	367 (44.0%)	0.63 (0.44-0.89)
Any Physical Health Outcome	161 (96.4%)	739 (88.5%)	3.49 (1.50-8.09) ¹

Note: URR, unadjusted relative rate; CAD, coronary artery disease; HTN, hypertension; TRM, total respiratory morbidity

¹Significant, p < 0.05

Table 3: Pre- and post-NF comparisons between cases (N=167) and matches (N=835)

Outcome	2 years Pre NF ARR (95% C. I.)	Pre-Post Period × Group Interaction	Post NF ARR (95% C. I.)
Arthritis	1.33 (1.23-1.47)*	0.77	1.36 (1.27-1.45) ¹
Cancer	1.20 (0.69-2.09)	0.99	1.20 (0.81-1.78)
CAD	1.31 (0.77-2.24)	0.64	1.46 (1.03-2.07) ¹
Diabetes	1.91 (1.45-2.52)*	0.02	1.43 (1.13-1.79) ¹
Fractures	1.71 (1.06-2.76)*	0.34	1.31 (0.95-1.82)
HTN	1.05 (0.80-1.38)	0.65	0.98 (0.82-1.19)
TRM	1.01 (0.76-1.34)	0.039	0.72 (0.57-0.92)
Any Physical Health Outcome	1.19 (1.09-1.29)*	0.027	1.08 (1.04-1.13) ¹

Note: CAD, coronary artery disease; HTN, hypertension; TRM, total respiratory morbidity, ARR, adjusted relative rate; C. I., confidence interval.

¹Significant, p < 0.05

Figure 1: CONSORT diagram

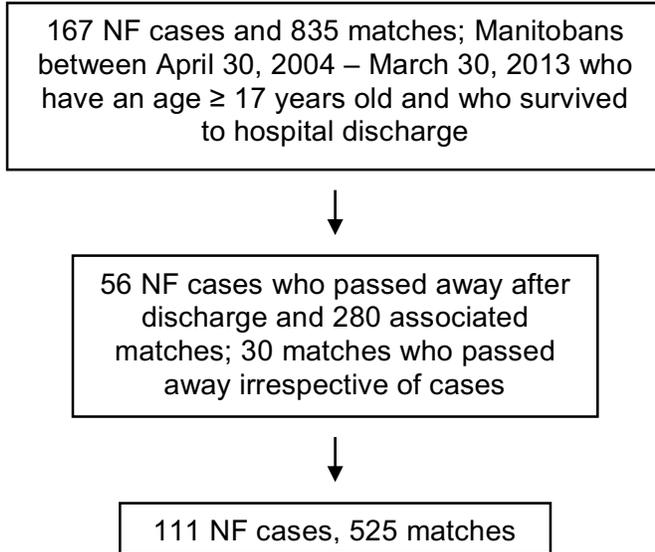


Table 4: Comparison of the descriptive characteristics and outcomes in NF survivors to NF subjects who survived to discharge but passed away in post period.

	<i>Surviving NF Cases (n=111)</i>	<i>Deceased NF Cases (n=56)</i>	<i>Test Statistic</i>	<i>P value</i>
Age	45.6 ± 15.8 (17-87)	57.7 ± 12.2 (30-89)	-5.44	<0.001
Gender (male)	57 (51.4%)	26 (46.4%)	0.36	0.55
Physical ADG	4.9 ± 3.2 (0-15)	5.8 ± 3.2 (0-13)	-1.75	0.08
%TBSA	5.7 ± 6.3% (0.01- 35.0) ^a	5.5 ± 4.3% (0.05- 20.0) ^b	0.21	0.84
LOS	34.0 ± 40.9 (2-252)	43.4 ± 40.8 (1-218)	-1.39	0.17
ICU stay (yes/no)	45 (40.5%)	34 (60.7%)	6.08	0.01
ICU, days	2.9 ± 5.6 (0-27.2)	6.8 ± 10.8 (0-57.7)	-2.53	0.01
Duration of Follow Up, years	6.1 ± 2.2 (1.5-10.9)	2.1 ± 2.4 (0.003-10.2)	10.56	<0.001
Time to death, years	-	2.1 ± 2.4 (0.003-10.2)	-	-
OUTCOMES*				
Number of procedures	2.6 ± 1.2 (1-7)	2.8 ± 1.7 (1-9)	-0.73	0.47
Skin Graft	73 (65.8%)	28 (50.0%)	3.87	0.049
Amputation	12 (10.8%)	11 (19.6%)	2.44	0.12

Note: ADG: aggregate diagnostic groups; TBSA, total body surface area; LOS, length of stay; ICU, intensive care unit

^an=107

^bn=51

*Sum does not equal 100% as some individuals had multiple outcomes or were closed primarily.

Figure 2: Rate of Death After NF Index Date (n=56)

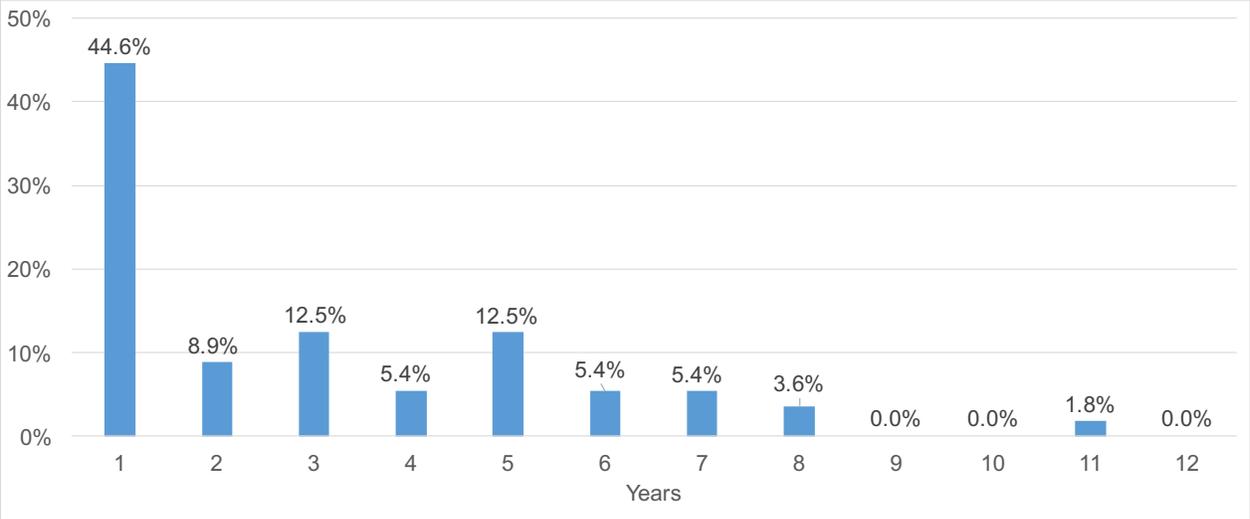


Table 5a: Rates of physical health outcomes of cases compared with matches, in the years following the NF index date

<i>Outcome</i>	<i>Case (n=111)</i>	<i>Match (n=525)</i>	<i>URR (C.I. 95%)</i>
Arthritis	106 (95.5%)	365 (65.7%)	11.06 (4.43-27.61) ¹
Cancer	17 (15.3%)	60 (10.9%)	1.48 (0.83-2.67)
CAD	19 (17.1%)	48 (8.6%)	2.20 (1.23-3.94) ¹
Diabetes	46 (41.4%)	128 (22.3%)	2.47 (1.61-3.79) ¹
Fractures	29 (26.1%)	80 (14.5%)	2.09 (1.28-3.40) ¹
HTN	51 (46.0%)	228 (41.0%)	1.23 (0.81-1.85)
TRM	43 (38.7%)	231 (41.7%)	0.88 (0.58-1.34)
Any Physical Health Outcome	suppressed, ~100%		6.00 (1.86-19.39) ¹

Note: URR, unadjusted relative rate; CAD, coronary artery disease; HTN, hypertension; TRM, total respiratory morbidity

¹Significant, $p < 0.05$

Table 5b: Relative rates of physical health outcomes of cases compared with matches, 2 years before NF index date

<i>Outcome</i>	<i>Case (n=111)</i>	<i>Match (n=525)</i>	<i>URR (C.I. 95%)</i>
Arthritis	68 (61.3%)	208 (39.6%)	2.41 (1.58-3.67) ¹
Cancer	7 (6.3%)	29 (5.5%)	1.15 (0.49-2.70)
CAD	8 (7.2%)	22 (4.2%)	1.78 (0.77-4.10)
Diabetes	28 (25.2%)	72 (13.7%)	2.12 (1.29-3.48) ¹
Fractures	18 (16.2%)	36 (6.9%)	2.63 (1.43-4.83) ¹
HTN	26 (23.4%)	132 (25.1%)	0.91 (0.56-1.47)
TRM	29 (26.1%)	121 (23.1%)	1.18 (0.74-1.89)
Any Physical Health Outcome	92 (82.9%)	341 (65.0%)	2.46 (1.47-4.11) ¹

Note: URR, unadjusted relative rate; CAD, coronary artery disease; HTN, hypertension; TRM, total respiratory morbidity

¹Significant, $p < 0.05$

Table 6: Pre- and Post-NF comparisons between cases (n=111) and matches (n=525)

<i>Outcome</i>	<i>2 years Pre NF ARR (95% C. I.)</i>	<i>Pre-Post Period × Group Interaction</i>	<i>Post NF ARR (95% C. I.)</i>
Arthritis	1.41 (1.31-1.53)	0.60	1.49 (1.23-1.80) ¹
Cancer	1.54 (0.91-2.60)	0.38	1.08 (0.45-2.59)
CAD	1.80 (1.07-3.04)	0.84	1.68 (0.76-3.75)
Diabetes	1.81 (1.36-2.41)	0.76	1.72 (1.15-2.59) ¹
Fractures	1.70 (1.18-2.45)	0.40	2.22 (1.30-3.77) ¹
HTN	1.19 (0.95-1.50)	0.33	1.00 (0.69-1.47)
TRM	0.92 (0.71-1.19)	0.26	1.14 (0.80-1.62)
Any Physical Health Outcome	1.14 (1.08-1.19)	0.039	1.28 (1.14-1.43) ¹

Note: CAD, coronary artery disease; HTN, hypertension; TRM, total respiratory morbidity, ARR, adjusted relative rate; C. I., confidence interval.

¹Significant, $p < 0.05$