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Project Title: **Mental Disorders of Necrotizing Fasciitis Compared to Matched Controls: A Longitudinal Study**

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Summary (250 words max single spaced):

Necrotizing fasciitis (NF) is associated with extensive surgery, amputations, and prolonged hospitalization. Patients who suffer other traumatic injuries such as burns have increased psychopathology. NF is often more severe than burns and therefore it is conceivable that NF survivors will have an increased rate of mental disorders post-discharge. This study is a longitudinal, population based cohort study with matched controls (1:5) using administrative data obtained from MCHP. Mental disorder rates in the NF cohort were compared to controls for the 2-year period post infection date (index date) and also compared to the preexisting rates for the 2-year period prior to the index date. Disorders of interest include depression, anxiety, substance misuse and any mental disorder. The model was adjustment for age, sex, location of residence, income and pre-existing morbidity. First, the effect of NF on mental health was studied. There were higher rates of mental disorders in the NF compared to controls post infection. Next, a comparison of how this rate changed over time was done. After adjusting for age, sex, location of residence, income and pre-existing morbidity, it was found that the relative rates of mental disorders post infection compared to pre-infection increased similarly for cases and controls ($p = 0.07$). However, the NF population has a higher rate of mental disorders prior to hospital admission compared to controls therefore hospital admission should be used as an opportunity to screen and treat NF patients.

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Mental Disorders of Necrotizing Fasciitis Compared to Matched Controls: A Longitudinal Study

Submitted in partial fulfillment of requirements for BSc. Med Program, August 6, 2017

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Abstract

Necrotizing fasciitis (NF) is associated with extensive surgery, amputations, and prolonged hospitalization. Patients who suffer other traumatic injuries such as burns have increased psychopathology. NF is often more severe than burns and therefore it is conceivable that NF survivors will have an increased rate of mental disorders post-discharge. This study is a longitudinal, population based cohort study with matched controls (1:5) using administrative data obtained from MCHP. Mental disorder rates in the NF cohort were compared to controls for the 2-year period post infection date (index date) and also compared to the preexisting rates for the 2-year period prior to the index date. Disorders of interest include depression, anxiety, substance misuse and any mental disorder. The model was adjustment for age, sex, location of residence, income and pre-existing morbidity. First, the effect of NF on mental health was studied. There were higher rates of mental disorders in the NF compared to controls post infection. Next, a comparison of how this rate changed over time was done. After adjusting for age, sex, location of residence, income and pre-existing morbidity, it was found that the relative rates of mental disorders post infection compared to pre-infection increased similarly for cases and controls ($p = 0.07$). However, the NF population has a higher rate of mental disorders prior to hospital admission compared to controls therefore hospital admission should be used as an opportunity to screen and treat NF patients.

Introduction

Necrotizing fasciitis (NF) is an acute soft tissue infection of the fascia and is associated with extensive surgery, amputations, and prolonged hospitalization that has been associated with increased stress and deleterious consequences [1]. Mental health, defined as a person's condition with regard to their psychological and emotional well-being, may be affected by this stress. The effect of NF on subsequent mental health has not been studied.

Traumatic injuries, such as those leading to amputations, can result in patients with functional impairment and disability associated with a negative impact on mental health. An observational study on patients who suffered traumatic injury reported major depression and generalized anxiety as the most common complaints in survivors [2]. Furthermore, traumatic injuries often result in increased time spent in the intensive care unit (ICU). A previous study assessing the mental health of patients immediately after discharge from the ICU indicated that many patients experienced anxiety and depression post discharge [3]. Therefore, it is conceivable that NF survivors, many of whom receive extensive surgeries, amputations and prolonged hospital stay often including admission to an ICU[4], will have an increased risk of mental disorders.

Similar to NF, burns also damage to the skin and soft tissues and are treated with emergent surgical debridement, fluid and nutritional support [5]. Research has found that there is a higher rate of depression following burn injury. NF is more traumatic than burns in that, even with the same size of injury as a burn, NF patients require more surgical intervention, ICU care and longer hospital stays [4]. Since the effects of NF are more severe compared to burns, it is

expected that there will also be an increased relative rate of mental disorders in NF patients post infection.

Objectives

The objective of this study is to examine whether or not there is an increased relative rate of mental disorders two years following an NF episode, compared to the two years pre-infection. The mental disorders studied include anxiety, depression, and substance abuse (alcohol and drug use). Population level data from Manitoba Center for Health Policy (MCHP) and the clinical NF registry was used to compare NF cases to controls (1:5) matched on age, sex and degree of comorbidity. The relative rate of mental disorders will be compared between cases and matches in the pre NF period, the post NF period, and between the pre and post period adjusting for sex, household income (defined as high versus low income based on income quintiles with the lowest 2 quintiles and income "not found" termed "poor"), location of residence and pre-existing co-morbidities.

Methods

Data Sources
Approvals for this study were granted from the University of Manitoba Health Research Ethics Board and Manitoba Health - Health Information Privacy Committee (*HIPC No. 2014/2015 – 54*). This population-based epidemiological study utilized provincial administrative health data from the Population Health Research Data Repository, managed by the University of Manitoba's Manitoba Centre for Health Policy (MCHP). This data repository is distinct, as it holds de-identified individual level data regarding the population of Manitoba from 1984 [6]. Through a scrambled health information number, patients' characteristics can be linked across various data sets in an anonymous fashion. The use and reliability of the MCHP data for Manitoban individuals has been previously validated [7]. International Classification of Disease (ICD-9) coding was utilized to identify diagnoses from physician billing claims, Vital Statistics, and hospital discharge abstracts. This administrative data was linked to the NF component of the Burn Registry at the Health Sciences Centre in Winnipeg, Manitoba, Canada. This clinical registry contains information on NF patients in the province that receive treatment at the two referral centers in the province.

Study Population
Patients ≥18 years in the NF registry at two regional referral centers were selected if they had a diagnosis of NF between January 1, 2004 and December 31, 2014. NF cases were identified from health records using methodology previously reported [8]. Confirmation of NF diagnosis was based on evidence of fascial involvement reported by the surgeon at the time of surgical debridement. NF cases were matched 1:5 to a control cohort based on age on the index date (within a year), sex, geographic residence and physical aggregated diagnostic groupings (PADG). PADGs are calculated using the adjusted clinical group (ACG) system, developed at Johns Hopkins [9] .The ACG system assigns individuals to 1 of 32 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 their level of comorbidity that takes into account measures of not just the presence of a comorbidity but also the effect of the comorbidity.

The Province of Manitoba is divided into 5 Regional Health Authorities (RHAs), which were utilized to match individuals based on geographic residence. Matching was based on NF case age at the index date, sex, health region (based on postal code), and PADG groupings (0, 1-2, 3-5, 6+). Matching based on the specific number of PADGs resulted in only 85% successful matches, whereas matching using PADG grouping resulted in 100% of successful matches. A total of 1030 individuals were matched to 206 cases.

Time Frame
January 1, 2004 was the earliest possible index date in the study and March 31, 2014 the latest possible with a minimum of two years of follow-up. Cohorts were compared for mental disorders 730 days prior to the index date ("pre") up to 730 days after the NF index date. Patients who died within the 730 days of the NF index date were included in this study.

Outcome Variables
The presence of mental disorders in the study population were examined, as coded using the International Classification of Diseases-9-clinical modification (ICD-9-CM) and -10-CA, an enhanced version of ICD-10 developed for morbidity classification in Canada. The codes used were: anxiety: [ICD-9-CM]: 300.0, 300.2, 300.3; [ICD-10-CA]: F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F431; depression: [ICD-9-CM]: 296.2-296.3, 296.5, 300.4, 309, 311; [ICD-10-CA]: F31.3-F31.5, F32, F33, F341, F380, F381, F432, F438, F530 and substance abuse which includes both alcohol and drug abuse: [ICD-9-CM]: 291, 292, 304, 305, 303; [ICD-10-CA]: F10-F19, F55 [10]. A variable "any mental disorder" was created and includes one or more of anxiety, depression or substance abuse. Disorders were based on validated diagnostic definitions for the Manitoban population [7,11].

Statistical Analysis
All data extraction and analysis was performed using SAS (Version 9.3, Cary, NC, USA). Comparisons of demographics between cohorts were determined by Pearson's chi square test or Student's t-test. A propensity score was generated from bias-reduced logistic regression model based on covariates including age (continuous) as well as binary indicators for sex, urban-versus rural residence, high versus low income, PADG over/under the median of four and mental aggregated diagnostic groupings (MADG) over/under the median of 1 [9]. Comparisons of individual propensity score distributions showed sufficient overlap, and suggested that application of the weights of inverse probability of treatment (IPTW), resulted in cohorts in which the distribution of variables were comparable between cases and matches; hence comparisons between treatment groups was feasible. Logistic regression models were built and unadjusted relative ratios (URR) and adjusted relative ratios (ARR) were then determined by generalized estimating equations (GEE) with a Poisson distribution. The weights establish estimates representing population average treatment effects with optimal balance between the cases and matches[12]. In addition, a time offset (log person-years) was included to account for the effect of time in the study by each participant (i.e. if they exited the study before the end date) in the GEE model.

Results

Descriptive characteristics of 206 NF cases and 1030 matches are shown in **Table 1**. There was no significant difference regarding to age, sex distribution, location of residence (urban vs. rural) or PADG groupings, which establishes that matching was successful. PADG groupings showed that a PADG score range of 6+ was the most common group, indicating the high rate of pre-existing co-morbidity in the NF group. There was a significantly greater proportion of cases with poor individuals as compared to the matches ($p<0.01$) There was also a significant

difference with regards to follow up years between cases (4.7 years) versus matches (6.5 years).

A comparison of the unadjusted relative rates (URR) of mental disorders two years following the index date for cases and matches are shown in **Table 2a**. Cases have a significantly higher ($p < 0.05$) URR for depression, substance abuse and any mental disorder compared to matches.

Comparisons between two years prior to index date compared to the two years post NF index date were then analyzed for 206 NF cases and the 1030 matches in **Table 3.** The pre-existing rate of mental disorders was compared to the post-infection rate. A pre-post "period x group" interaction was used to determine if there was a change in the adjusted relative rates in the cases compared to the matches over time. Since there was a difference in mortality and therefore the duration of follow up, in the final GEE we included a time offset which accounts the contribution of an individual relative to how long they are in the study. No single mental disorder significantly changed over time. However, the interaction term for any mental disorder trends towards significance ($p = 0.07$).

Discussion

This is the first population based study on the long term mental disorders in NF survivors. The NF cohort was matched based on age, sex, location of residence and pre-existing physical comorbidities. We found a significantly larger proportion of NF cases with lower income compared to the matches. The Canadian Mental Health Association has found that lower income can impact mental health as loss of resources such as income, employment, and transient housing can exacerbate for mental illness and contribute to relapse [13]. A significant association has been found between the depression and low income [14]. Also, poverty has been a risk factor for the subsequent development of mental disorders [15]. Our study mirrors these findings and therefore further adjustments were established to adjust for these differences in study design. PADGs were utilized in this study to account for pre-existing comorbidities and the impact on subsequent mental illness. There have been multiple associations between mental health and chronic physical conditions due to their impact on quality of life and demands on healthcare and other services [16].

The shorter length of follow up for NF patients can be explained by the increased mortality rate in the NF population as compared to controls. One study found that NF patients who survive to discharge have a significantly higher mortality rate compared to age and gender matched controls from the general population. For example, a NF patient at age 50 who survived to discharge had a decrease in life expectancy by 20-25 years [17]. In our study, a time offset (log person-years) was included in the GEE to compensate for individuals leaving the study before 730 days post NF index date due to mortality [18].

When the rate of mental disorders was examined in the post infection period only, we found a significantly higher relative rate in the cases compared to matched controls. Given the high pre-infection comorbidity further assessment of the relative rates of mental disorders in the two-year period post NF date compared to the two-year period prior to NF index date was undertaken. Using GEE, the relative rate of mental disorders in cases relative to matches in the post period relative to the pre-period was calculated. It was found that although the period x group interaction term for any mental disorder trended towards significance ($p = 0.07$) there was no significant change in relative rates of each mental disorder between cohorts over time. This is likely due to high pre-existing mental disorders in the NF population which was nearly 1.3 times greater for depression and 2.8 times for substance abuse in the pre-infection period compared

to controls.

We compared the rates of mental disorders in the NF cohort to Manitoba's current rate. A recent publication shows that the rate of mood and anxiety disorders within Manitoba was 23.3%. In the NF population, pre-existing rates of anxiety alone were 19.4% and depression alone 16.5%. The pre-existing rate of substance abuse was much greater in the NF cohort at 11.7% compared to the general population's rate of substance abuse at 5% [11]. These data contextualize the findings of our study, indicating that the NF cohort has a higher burden of mental illness than others in the province.

In our study, we found a high burden of mental illness in NF patients. Recent studies have suggested that an ICU stay may be involved in changes to a patient's mental health. Critically ill patients were found to have higher rates of mental disorders prior to their illness compared to the general population [19]. In addition, a review on prior health status revealed that pre-existing mental disorders may also predispose patients to increased mental disorders after a critical illness resulting in ICU admission [19]. A population based cohort study revealed that survivors of critical illness have a previously increased number of psychiatric diagnoses and psychoactive medication use, thus suggesting a possible role of psychiatric disease predisposing patients to critical illness [20]. What is unclear is whether or not the trajectory of mental illness is in fact due to NF alone or is due to global deconditioning that is observed in frail patients [21]. NF patients may also be at risk of increased mortality which remains understudied in this vulnerable population.

Burn survivors suffer similar injuries to NF patients, however to a lesser degree [4]. The mental health of burn survivors has been studied by our research group. The previous study revealed that the relative rate of mental disorders did not significantly change compared to controls matched on age and sex, when pre-burn mental health was taken into consideration. However, burn survivors were also found to be a vulnerable group of patients who were with increased rates of pre-burn psychopathology and need for care in the years prior to their burn [22]. These results prove similar to our NF study.

Limitations

Limitations of this study must be interpreted to better understand our results. Administrative data relies on physician claims and hospital abstract data therefore it is not possible to account for individuals who are unable to or do not seek medical care due to physical immobility, stigma from the scar or extent of the mental disorder. One of concerns of administrative data and the use ICD codes is that they are not diagnostic for these disorders but rather they reflect the physician's assessment at the time of billing. However, this coding is based on a clinician's assessment of the patient's complaints, which will be a similar process between the two cohorts. Evaluation of this assessment in the current manner has been validated in previous studies [22–25]. Next, only one ICD code is reported for physician billing, which may result in underreporting of mental disorders in those with multiple complex medical issues. Physical health issues may be taking precedence over mental issues [23]. For example, a physician who sees a patient managing complex diabetes with mild depression may focus on the diabetes and the associated treatment and not code for the depression. However, we believe that any possible treatment seeking and/or reporting bias is likely equal in both cases and matches because they are matched on their comorbidities and a universal healthcare system is in place so there no existing cost with resource utilization. Finally, 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. The groups of aging individuals with similar comorbidities may comparably trend

towards similar rates of mental disorders as time progresses from the NF index date. We also used a dichotomous variable to establish if a diagnosis was present or not therefore the extent of the disorder was not measured. We did a sensitivity analysis looking at the half year, one year and two years follow up period. There was no difference over time once pre-existing mental illness was taken into account.

Strengths

Manitoba is uniquely situated to perform such a study due to a high incidence of NF infections that are only referred to one of two sites. This permits inclusion of a large cohort of NF patients. The ability to match based on the degree of comorbidity allowed for a more accurate comparison better matches and controls, helping to delineate the effect specifically from the NF. Using a propensity score and IPTW in the analysis allowed the groups to be balanced to account for other possible confounding variables, permitting the equivalent of a post hoc randomization. Our study also utilized a time offset which accounts for the fact that individuals may exit the study before the end of the study period (i.e. die), as is shown by the different follow-up periods between the two cohorts. Thus, the individuals only contribute during the period of time they are in the study.

Future research should be directed to studying health status prior to NF infection and understanding associated susceptibility to this severe disease. Although no significant difference was found between the matches and controls post infection, a closer review taking into account health care utilization rates should be taken under consideration to better understand the impact.

Conclusion

In conclusion, NF patients appear to have a higher rate of mental disorders post infection compared to controls. However, this is related to their preexisting mental health status more than the presence or absence of NF. Given the higher rate of mental disorders, attention to mental health status prior should be a priority in NF patients. NF hospitalization may be an opportunity to engage patients in appropriate care. An outreach program to provide routine mental health screening and associated treatment should be offered to NF patients.

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Tables

Table 1a: Descriptive characteristics of NF cases and matches

Outcome	*Case (n=206)*	*Match (n=1030)*
Age	48 ± 16	48 ± 16
Sex (male)	105 (51.0%)	524 (51.0%)
Urban (%)*	99 (51.8%)	516 (53.6%)
Poor (%)**	112 (58.6%)[1]	399 (41.5%)
Follow up, years	4.7 ± 2.8[1]	6.5 ± 2.8
PADG score		
0	11 (5.3%)	55 (5.3%)
1-2	55 (26.7%)	275 (26.7%)
3-5	56 (27.2%)	280 (27.2%)
6+	84 (40.8%)	420 (40.8%)

Data shown as mean ± s.d. or count (%).
[1]Significant difference, $p < 0.05$
*Urban vs rural: n = 191 cases, n = 962 matches
**Rich vs poor: n= 191 cases, n = 962 matches
Note: PADG, physical aggregated diagnosis groups; TBSA, total body surface area; NA, not applicable

Table 1b: Injury characteristics of NF patients

TBSA, %	3.0 (1.8, 7.0)
Length of stay, days	22 (14, 51)
Procedures	2 (2, 3)
Amputation	25 (12.2%)
Free tissue transfer	12 (5.9%)
Skin graft	127 (62.0%)
Other closure	79 (38.0%)

Data shown as mean ± s.d. or count (%).
Sum of proportions > 100% as patients had ≥ 1.

Table 2a: Rates of mental health disorders of cases and matches, 2 years following the NF index date

Disorder	*Case (n=206)*	*Match (n=1030)*
Anxiety	42 (20.4%)	182 (17.7%)
Depression	40 (19.4%)	133 (12.9%)
Substance Abuse	19 (17.1%)	48 (8.6%)
Any Mental Health Disorder	74 (35.9%)	263 (25.5%)

Table 2b: Rates of mental health disorders of cases and matches, 2 years before NF index date

Disorder	*Case (n=206)*	*Match (n=1030)*
Anxiety	40 (19.4%)	207 (20.1%)
Depression	34 (16.5%)	132 (12.8%)
Substance Abuse	24 (11.7%)	43 (4.2%)
Any Mental Health Disorder	68 (33.0%)	291 (28.3%)

Table 3: Pre- and post-NF comparisons between cases (N=206) and matches (N=1030)

Disorder	*2 years Pre NF URR (95% C.I.)*	*2 years Pre NF ARR (95% C.I.)*	*Pre-Post Period x Group Interaction*	*2 years Post NF URR (95% C.I.)*	*2 years Post NF ARR (95% C.I.)*
Anxiety	0.96 (0.67-1.40)	1.20 (0.85-1.68)	0.27	1.19 (0.82-1.74)	1.50 (1.07-2.10)
Depression	1.34 (0.89-2.03)	1.35 (0.92-1.99)	0.13	1.63 (1.10-2.40)[1]	1.80 (1.26-2.57)
Substance Abuse	1.79 (1.79-5.11)[1]	2.41 (1.58-5.07)	0.77	2.96 (1.72-5.10)[1]	2.75 (1.63-4.63)
Any Mental Health Disorder	1.25 (0.91-1.72)	1.44 (1.10-1.82)	0.07	1.63 (1.19-2.25)[1]	1.81 (1.42-2.30)

Note: URR, unadjusted relative rate; ARR, adjusted relative rate; C. I., confidence interval; PADG, physical aggregated diagnosis groups; MADG, mental aggregated diagnosis groups
ARR adjusted for age, sex, income, PADG, MADG
[1]Significant difference, $p < 0.05$