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**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 75599

**Manuscript Type:** ORIGINAL ARTICLE

*Retrospective Cohort Study*

**Decreased incidence of febrile neutropenia in Michigan following masking and social distancing orders for the COVID-19 pandemic: A population based cohort study**

Decreased Febrile Neutropenia with Masking

**Abstract**

**BACKGROUND**

It has been theorized that 75-80% of febrile neutropenia is caused by endogenous pathogens, while up to 20% of cases are thought to be caused by a viral infection. It is unknown if precautions such as masking and social distancing reduce the risk of febrile neutropenia in susceptible populations.

**AIM**

To determine whether COVID-19 infection mitigation efforts, namely masking and social distancing, was associated with a reduction in the incidence of febrile neutropenia (FN).

**METHODS**

This was a retrospective population based cohort study comparing the incidence of FN in the 13 mo prior to (Year 0) and 13 mo following (Year 1) the public health executive orders (PHEO) in Michigan. Data was queried for all emergency department (ED) visits from April 1st, 2019 to March 31st, 2021 from the National Syndromic Surveillance Program (NSSP), a program which collects data that is voluntarily submitted by

approximately 89% of Michigan EDs. The primary study outcome was the incidence of FN as a proportion of emergency department visits in the 13-months before and 13-months after COVID-19 mitigations efforts, namely masking and social distancing. We hypothesized that there would be a significant decrease in the incidence of FN in the period following the PHEO aimed at reducing the spread of the SARs-CoV-2 virus.

## RESULTS

There was a total of 8,979,221 total ED visits captured during the study period. In Year 0 there were 5,073,081 recorded ED visits and 3,906,140 in Year 1. There was a significant reduction in the proportion of total ED visits with a diagnosis of FN, decreasing 13.3% across periods (0.15% vs. 0.13%,  $P = 0.036$ ). In patients with a hematologic malignancy a more impressive reduction in the incidence of FN was evident following PHEO (22% vs 17%,  $P = 0.02$ ).

## CONCLUSION

We found a significant association between social distancing and mask guidelines implemented on a large public scale with decreased rates of FN, particularly in those with a hematologic malignancy. These findings may be useful in the design of future research and recommendations regarding the prevention of FN.

**Key Words:** Febrile Neutropenia; COVID-19; SARs-CoV-2; Malignancy; Hematology; Public Health

Baracy Jr. MG, Hagglund K, Kulkarni S, Afzal F, Arends K, Morris RT, Solomon LA, Aslam MF, Corey L. Decreased incidence of febrile neutropenia in Michigan following masking and social distancing orders for the COVID-19 pandemic: A population based cohort study. *World J Clin Oncol* 2022; In press

**Core Tip:** There has been a proven reduction in respiratory viruses (e.g. flu, common cold, *etc.*) with the implementation of social distancing and masking in the effort to prevent the spread of COVID-19. Although it has been theorized that 75-80% of febrile neutropenia is caused by endogenous pathogens, up to 20% of cases are thought to be caused by a viral infection. The primary purpose of this study was to evaluate the effect of widespread public health measures, namely masking and social distancing, on the incidence of febrile neutropenia. This retrospective cohort study found a significant reduction in the incidence of febrile neutropenia in the 13 mo following the implementation of public health interventions (masking and social distancing) compared to the 13 mo prior to these interventions- a decrease of approximately 13%. This was especially true for hematologic malignancies, for which there was a 22% reduction in febrile neutropenia.

## **INTRODUCTION**

Febrile neutropenia (FN) is defined as neutropenia in the setting of a temperature greater than or equal to 100.4 degrees Fahrenheit and is one of the most common and costly complications associated with cancer treatment<sup>1,2</sup>. Granulocyte colony stimulating factor (GCSF) is the most effective prophylaxis against neutropenia and the progression to FN<sup>3,4</sup>. Yet, little is known about non-pharmacological strategies, such as masking, for the prevention of FN in at-risk populations.

Currently, FN prevention strategies include hand hygiene and the avoidance of sick contacts and crowds, however the impact of these efforts is uncertain<sup>5</sup>. Furthermore, the majority of FN with culture-proven bacteremia are thought to be the result of translocation of gut bacteria<sup>6</sup>. Although it has been theorized that 75-80% of febrile neutropenia is caused by endogenous microorganisms, up to 20% of cases are thought to be caused by communicable pathogens, such as virions<sup>7</sup>. Accordingly, mitigating viral infection in at risks populations would theoretically reduce the incidence of FN. However, we are not aware of any population-based studies evaluating the impact of infection mitigation practices on the incidence of FN.

The public health crisis due to COVID-19 and its corresponding public health interventions provided a unique opportunity to evaluate the impact of social distancing and masking on the incidence of FN. In March of 2020, the state of Michigan issued an Executive Order that urged residents to remain at home and socially distanced, which was added shortly thereafter to include a mask mandate<sup>8</sup>. The aim of our study was to evaluate the association of these mitigation efforts and the incidence of FN in patients presenting to emergency departments (EDs) in the state of Michigan.

## **MATERIALS AND METHODS**

This is a retrospective cohort study comparing the incidence of FN in the 13 mo prior to (Year 0, March 1, 2019 – March 31, 2020) and the 13 mo following (Year 1, April 1, 2020 – April 31, 2021) the public health executive orders (PHEO) in Michigan. Approximately 89% of EDs across Michigan voluntarily submit encounter data (patient's chief complaint, associated diagnoses, age, sex, intake temperature, intake percent oxygen saturation, and blood pressure) to the National Syndromic Surveillance Program (NSSP). A query was made for all encounters with a diagnosis of Neutropenia (ICD-10-CM D70) from March 1, 2019 – April 31, 2021. Febrile neutropenia was defined as an intake temperature greater than or equal to 100.4 degrees Fahrenheit and an ICD-10-CM D70. The incidence of FN in Year 0 was compared to the incidence of FN in Year 1. To account for the impact of the COVID-19 pandemic on total ED visits, the incidence of each ICD code was analyzed as a proportion of ED visits for the corresponding year. Associated ICD-10-CM codes were grouped according to Clinically Relevant Groups (CRG) (Supplementary Table 1), modified from the Healthcare Cost and Utilization Project<sup>9</sup>. Analysis of the incidence of FN in each CRG was also performed. A visit containing multiple ICD-10-CM diagnostic codes was included in multiple CRGs, if applicable. This study was deemed exempt by the responsible institutional review board

### ***Statistical Analysis***

Descriptive statistics were generated to characterize the study cohorts. Continuous variables are described as the mean with standard deviation or median with range or interquartile range. Categorical variables are described as frequency distributions. Univariable analysis of factors associated with FN were assessed using Student's t-test, analysis of variance, and the chi-squared analysis. Multivariable analysis was done using logistic regression. Analyses were conducted using SPSS version 25.0 and a p-value less than 0.05 was considered statistically significant.

## **RESULTS**

From March 1st, 2019 to April 31st, 2021 there were 8,979,221 total ED visits in the state of Michigan with data submitted to the NSSP and at least one viable ICD-10 code. In Year 0, there were 5,073,081 recorded ED visits and 3,906,140 in Year 1, a decrease of 23%. There was a total of 5,717 encounters with a diagnosis consistent with neutropenia. There was a significant reduction in the proportion of total ED visits with a diagnosis of FN, decreasing 13.3% from Year 0 to Year 1 (0.15% vs. 0.13%, **p=0.036**).

In a sub-analysis of all patients with FN, in patients with a concomitant diagnosis of hematologic malignancy, FN was significantly lower in the period following PHEO (22% vs 17%, **p=0.02**, Table 2). In Year 0 there was a 29.3% incidence of FN in neutropenic patients with a CRG of hematologic malignancy, vs a 21.2% incidence in neutropenic patients without a CRG of hematologic malignancy (**p<0.0001**, Figure 1). This difference was not observed in Year 1 (23.8% vs 20.2%, *P* = 0.12). Hematologic malignancy was the only CRG diagnosis to have a relatively higher rate of FN in Year 0 compared to Year 1.

## **DISCUSSION**

The public health response to COVID-19 in the state of Michigan provided a unique opportunity to analyze the impact of social distancing and masking on the incidence of FN. Masking and social distancing designed to prevent the spread of COVID-19 have resulted in the decline of other non-covid viral illnesses<sup>10,11</sup>. Our study is the first to

document an association between this phenomenon and a decline in the incidence of FN, both overall and in patients with an ICD-10-CM diagnosis consistent with hematologic malignancy.

In the majority of cases, the underlying cause of FN is unknown, and therefore little is known about the efficacy of non-pharmacological efforts to prevent development of FN in neutropenic patients<sup>12</sup>. We found a significant association between the implementation of public health measures to prevent the spread of communicable diseases and the incidence of FN associated with hematologic malignancies. This is an important finding as patients with hematologic cancers are particularly vulnerable to FN and its associated morbidity and mortality<sup>13</sup>. Our findings suggest that a significant proportion of FN in patients with malignancy may have a viral etiology. Accordingly, health measures, such as masking, may reduce the risk of FN in vulnerable patients.

### *Strengths and Limitation*

The strengths of this study include a large number of encounters and associated accurate objective data points (ICD codes and temperature). Additionally, Michigan adopted the stay-at-home orders and mask mandates quickly and broadly, with one of the highest compliance rates of the country during Year 1 (**Supplemental Figure 1**)<sup>14</sup>. As a result, our results likely accurately reflect the effect of COVID-19 mitigation efforts on FN.

Our study has several limitations in addition to the inherent vulnerability to unmeasured biases found in retrospective studies: 1) There may be a small number of encounters of FN that are missed in this dataset; 2) Only the intake vital signs were available, and a temperature of 100.4°F was selected as the cutoff for diagnosing FN (rather than 101°F) in an effort to have a more inclusive cohort; 3) Each ED visit was treated as a separate encounter. Therefore, a patient with FN who presented to the ED on multiple occasions would be captured multiple times; 4) It is impossible to account for individual patient hesitancy on presenting to ED<sup>14</sup>; 5) Charts review was not

possible, so the effect of active myelosuppressive therapy could not be assessed; 6) The number and identify of facilities contributing data changes over time, and the use of diagnosis codes could be inconsistent across and within facilities.

## **CONCLUSION**

Our study found a significant association between the implementation of social distancing and mask guidelines and the incidence of FN in ED patients with neutropenia. This reduction was most pronounced in those with a hematologic malignancy. These findings may be useful in the design of clinical trials as well as informing future recommendations for the prevention of febrile neutropenia in vulnerable patients.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

It has been theorized that 75-80% of febrile neutropenia is caused by endogenous pathogens, while up to 20% of cases are thought to be caused by a viral infection. It is unknown if precautions such as masking and social distancing reduce the risk of febrile neutropenia in susceptible populations.

### ***Research motivation***

There has been a proven reduction in respiratory viruses (e.g. flu, common cold, *etc.*) with the implementation of social distancing and masking in the effort to prevent the spread of COVID-19. We sought to elucidate whether such public health measures would concomitantly reduce the risk of febrile neutropenia in susceptible populations, namely those with malignancies.

### ***Research objectives***



To determine whether COVID-19 infection mitigation efforts, namely masking and social distancing, was associated with a reduction in the incidence of febrile neutropenia (FN).

### ***Research methods***

This is a retrospective population based cohort study comparing the incidence of FN in the 13 mo prior to and 13 mo following the public health executive orders in Michigan. Data was queried for all emergency department visits from April 1st, 2019 to March 31st, 2021 from the National Syndromic Surveillance Program (NSSP).

### ***Research results***

There was a significant reduction in the proportion of total ED visits with a diagnosis of FN, decreasing 13.3% across periods (0.15% vs. 0.13%,  $P = 0.036$ ). In patients with a hematologic malignancy a more impressive reduction in the incidence of FN was evident following PHEO (22% vs 17%,  $P = 0.02$ ).

### ***Research conclusions***

Masking and social distancing appear to decrease the risk of febrile neutropenia in susceptible populations, especially among patients with hematologic malignancies.

### ***Research perspectives***

Masking and social distancing appear to decrease the risk of febrile neutropenia in patients with malignancies, supporting the theory that a proportion of febrile neutropenia may be secondary to communicable infectious particles. Well-designed studies and clinical trials are needed to guide recommendations regarding masking and social distancing for the prevention of febrile neutropenia in vulnerable patients.

## ***1 KNOWLEDGEMENTS***

We would like to acknowledge the staff from the MDHHS for their help in data collection and management, especially Justin Henderson.

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