Burden of Opportunistic Infections in Hospitalized Patients with MS

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated central nervous system disorder that requires immunomodulating or immunosuppressive disease modifying therapies (DMTs). As with all immunosuppressive therapies, those used to treat MS carry the risk of opportunistic infections (OIs).[1] An OI is defined as either (1) an infection that does not cause disease in healthy people but becomes pathogenic in those with an impaired immune system or (2) an unusually severe infection caused by routine pathogens. In MS clinical trials, the OIs reported include progressive multifocal leukoencephalopathy, herpes virus infections, hepatitis B virus infection, and disseminated tuberculosis.[2-9] However, based on the mechanism of action of the DMTs, it is likely that other OIs may also be a concern. Case series and case reports of patients with MS have also identified OIs such as cryptococcus, Kaposi sarcoma, toxoplasmosis, pneumocystis pneumonia, nocardiosis, and listeriosis.[10-21]

A recent study by Gahedri et al found that infection related hospitalizations were 3-5 times higher in people with MS than the general public.[22] This is unsurprising given that infections can lead to worsening MS symptoms, especially in the case of fever.[23] Immunocompromised patients are at an increased risk of OIs when hospitalized, however this risk is expected to be even greater when the admitting diagnosis is an infection. A nationwide cohort study in Sweden showed that MS patients have a higher risk of OIs than the general population,[24] but it is unknown if the higher risk of infection may be confounded by the added risk of hospitalization.

To our knowledge, there are no population-based studies that compare the incidence of hospital acquired OIs among MS patients vs non-MS patients in the US. The primary objective of this study was to compare the risk of hospital acquired OIs in patients with MS vs non-MS who's primary diagnosis was not an infection that put them at risk for a hospital acquired OI. The secondary objective was to compare the overall risk of OIs in hospitalized patients (non-primary diagnosis).

Methods

Data Source

A cross-sectional, population-based, secondary analysis of the 2018 data from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) was performed. NIS is the largest publicly available all-payer database of US hospitalized patients and approximates 97% of discharges from US hospitals. The NIS is a stratified sample of hospitals drawn from the subset of hospitals in 48 states that can be matched to the American Hospital Association (AHA) survey data. The strata are based on region, location/teaching status, bed size, and ownership. From the 60 strata, 20% of the hospitals are randomly drawn and 100% of the discharges from the sampled hospitals are included (>7 million hospitalizations). The discharge weights are constant for all discharges within each stratum, and therefore, the sum of all the sample weights in each stratum represents the total number of discharges reported in the AHA survey (>35 million hospitalizations). Data from each record contains information regarding patient demographics, diagnoses (40 ICD-10-CM codes), procedures, and other information associated with a hospital admission. The study was considered exempt by the Institutional Review Board, as HCUP-NIS database is a publicly available and nonidentifiable data source.

Population and Variables

Adult (age ≥18) patients were included if their primary diagnosis code was not for an OI or another infection that increases the risk for an OI (ICD-10 code beginning with ‘A’, ‘B’, ‘J00-J22’, L00-L08, or ‘N39.0’). The ICD-10-CM codes for OIs can be found in the appendix. The MS cohort was identified based on the presence of an ICD-10-CM code ‘G35’. The control group constituted those without a diagnosis code for MS. The primary outcome was a secondary diagnosis for a hospital acquired OI. The secondary outcome was secondary diagnosis for any type of OI.

Patient and Hospital characteristics

Patient and hospital level covariates were already provided in the NIS database. Patient-level covariates included demographics (age, sex, race, primary payer, rural urban code, census region, median household income), admission status (elective or non-elective), and presence of an ED record. The hospital characteristics included location/teaching status, bed size, and ownership. To further reduce selection bias, we utilized the Elixhauser comorbidity software (ECS) refined for ICD-10 CM diagnoses, v2021.1. ECS identifies 38 pre-existing conditions based on secondary diagnoses. From the ECS variables, we selected conditions more common in people with MS which have also been associated with poorer health outcomes. These variables included diabetes, hypertension, depression, and obesity. From the clinical classification software, we extracted the variables related to tobacco use and socioeconomic status.

Statistical Analyses

Given the complex sampling design of HCUP-NIS, statistical analyses were performed using PROC SURVEY procedures in SAS version 9.4, unless specified. In all statistical models, an alpha level of 0.05 was chosen. We compared the summary statistics using chi-square for categorical variables and Student's *t*-test for continuous variables. To identify independent predictors of OIs, multivariable logistic regression and modified Poisson models were developed. We used PROC SURVEYLOGISTIC to estimate adjusted odds ratios (OR) and PROC GENMOD to estimate adjusted prevalence ratios (PR). With the GENMOD procedure, we were able to account for in-hospital correlations, but not the complex clustered sampling methodology. We reported the effect estimates, P values, and 95% confidence intervals (CI).

Results

In 2018, approximately 25,806,394 adult patients were hospitalized with a non-infection related primary diagnosis. Of this study population, the MS cohort represented 0.47% (n=115,180). Figure 1 details the study population.

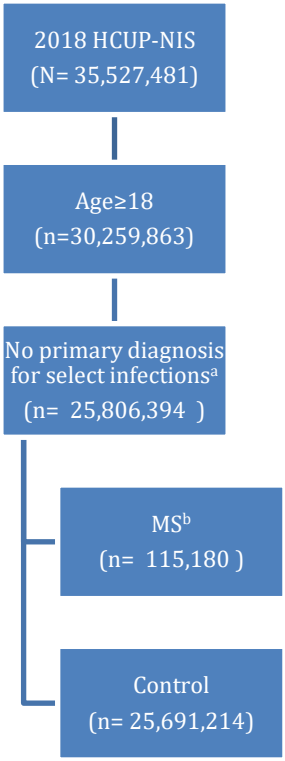

Figure 1 Study Population: [a]Select infections identified by ICD-10 code beginning with 'A', 'B', 'J00-J22', L00-L08, or 'N39.0'. The ICD-10-CM codes for OIs can be found in the appendix. [b]MS Identified by ICD-10 code 'G35'

Bivariate Analyses

The respective incidences of a secondary hospital OI in the MS and control groups were 0.93% (1,070/115,180) and 0.50% (129,175/25,691,214), resulting in an unadjusted RR of 1.848 (95% CI 1.620 to 2.108) unadjusted OR of 1.856 (95% CI 1.625 to 2.120). The respective incidences of any non-principal diagnosis OI in the MS and control groups were 12.04% (13,865/115,180) and 7.47% (1,919,695/25,691,214), resulting in an unadjusted RR of 1.611 (95% CI 1.553 to 1.671) and an unadjusted OR of 1.695 (95% CI 1.626 to 1.766).

Descriptive statistics

Table 1 details the characteristics of the study population, which were significantly different between the two groups.

Variation	MS	Control	P-value	Missing
n (weighted)	115,180	25,691,214		
Age in years (%)			<0.0001	0
18-34	10.66	20.43		
35-49	22.41	14.56		
50-64	36.56	23.31		
65-79	26.46	26.58		
80+	3.90	15.11		
sex (%)			<0.0001	483
male	25.97	41.73		
female	74.03	58.27		
Race (%)			<0.0001	131938
White	73.24	66.28		
Black	17.47	15.44		
Hispanic	6.21	11.79		
Other	3.08	6.58		
Primary payer (%)			<0.0001	7015
Medicare	55.19	45.66		
Medicaid	14.22	19.05		
Private	26.14	27.92		
Other	4.45	7.37		
Patient location (%)			<0.0001	28692
Large Central Metro	28.88	29.76		
Large Fringe Metro	27.08	24.02		
Medium Metro	20.55	20.76		
Small Metro	9.33	9.38		
Micropolitan	8.18	9.20		
Noncore	5.98	6.88		
Region (%)			<0.0001	0
Northeast	21.67	18.68		
Midwest	26.16	22.42		
South	34.57	39.50		
West	17.59	19.40		
Median Income Based on Zip Code (%)			<0.0001	90830
1 - 45,999	25.59	29.54		
46,000 - 58,999	26.93	26.98		
59,000 - 78,999	25.66	23.82		
79,000+	21.82	19.66		
Elective admission (%)			<0.0001	7355
No	80.85	73.95		
Yes	19.15	26.05		
ED record on file (%)			<0.0001	0
No	67.75	57.55		
Yes	32.35	42.45		
Hospital location/Teaching Status (%)			<0.0001	0
Urban teaching	73.78	71.16		
Urban non teaching	19.18	20.33		
Rural	7.03	8.50		
Hospital Control (%)			<0.0001	0
Voluntary	77.43	73.40		
Proprietary	12.49	15.06		
Public	10.08	11.54		
Hospital bedsize (%)			0.7163	0
Small	20.95	20.81		
Medium	28.75	28.99		
Large	50.30	50.20		
Comorbidities (%)			<0.0001	0
Diabetes	20.01	25.97		
Hypertension	49.71	51.16		
Depression	23.93	12.20		
Obese	18.13	17.18		
Tobacco use	19.31	16.76		
Outcomes n, (%)			<0.0001	0
Hospital aquired OI	1,070 (0.93)	129,175 (0.50)		
Any OI	13,865 (12.04)	1,919,695 (7.47)		

Table 1 Patient and Hospital Characteristics

Among the MS group, most hospitalizations occurred in white (73%) female (74%) patients aged 50-64 (37%) and on Medicare (55%). Conversely, the control group was older 56-79 (26%) with

more racial diversity (66% white), fewer females (58%), and less on Medicare (46%). The prevalence of depression was twice as high in the MS group compared to the control group (24% vs 12%).

Association between MS and Odds of a Secondary OI

Supplementary Table S2 details the results of the modified Poisson regression models and multivariable logistic regressions for evaluating the associations between MS and the risk and odds of developing an OI.

Compared to hospitalizations without MS, those with MS had a higher risk of both a secondary hospital acquired OI (RR 95% CI)--1.91 (1.67-2.12 and any type of OI (1.53 (1.47-1.59). Compared to hospitalizations without MS, those with MS had a higher odds of both a secondary hospital acquired OI (odds ratio 95% CI)-- 1.918 (1.677- 2.195) and any type of OI (1.613 (1.546 - 1.683))

Table 2 Adjusted and unadjusted associations between MS and OIs

Hospital OI	Estimate	95% CI
Adjusted RR	1.91	1.67-2.12
Adjusted OR	1.92	1.68-2.20
Unadjusted RR	1.85	1.62- 2.10
Unadjusted OR	1.86	1.63 - 2.12

Any OI	Estimate	95% CI
Adjusted RR	1.53	1.47-1.59
Adjusted OR	1.61	1.55-1.68
Unadjusted RR	1.61	1.55 - 1.67
Unadjusted OR	1.70	1.63-1.77

Discussion

In this population-based, national cohort study, patients with MS had an increased risk of OIs compared to those without MS. Only one other population-based study has supported this relationship, however it was conducted in Sweden,[23] where the risk of infection may be lower due to decreased use of the newer and more potent immunomodulating drugs.[22] Furthermore, their a-priori defined OIs were not as extensive, nor did they include hospital acquired OIs. Thus, our study contributes more extensive information on the burden of OIs and is applicable to the US population.

The implication of increased risk of OIs in MS patients is very important. Firstly, considering that MS patients are almost twice as likely to develop a hospital acquired OI, it is imperative that MS certified hospitals take high precautions with infection control. Specifically, infection control measures are most needed regarding catheters. Regarding any type of OI, MS patients are at more than a 50% higher risk. This information underscores the importance of ensuring that MS patients do not exceed the maximum allowable amount of time on specific DMTs, immunizations, testing for HBV, HCV, and tuberculosis before initiating therapy, and checking JC antibodies regularly for patients on natalizumab. Most importantly, the relationship between OIs and MS needs to be further studied, especially in the non-hospitalized population. This information may help construct prophylactic antimicrobial guidelines for MS patients given particular risk factors (eg medication, age, comorbidities).

The strengths of our study include large sample size, utilization of procedures to accommodate the complex sampling of the HCUP-NIS data and therefore the results represent the 2018 US population, and application of ECS software to adjust for relevant comorbidities. Furthermore, we controlled for the bias of that MS patients are more likely to be hospitalized for an infection than the general population.

This study was subject to many limitations. Firstly, the diagnostic codes that I used to identify OIs have not been shown to be valid in administrative datasets with positive predictive values. Second, due to the lack of granularity of ICD-10 codes, I was not able to include all types of OIs. For example, osteomyelitis is only considered an OI if it is caused by *S. Aureus, S. penuoniae,*

listeria, nocardia, pseudomonas, E. coli, Klebsiella, H. flu, or Serratia. The ICD-10 codes do not specify the causative pathogen for osteomyelitis, and therefore, we could not include it as an OI. Other OIs that it was not possible to determine based on the granularity of ICD-10 codes include >1 month duration of diarrhea with Rotavirus and Norovirus and >1 month duration of Cryptosporidiosis, Giardia, microsporidium. Furthermore, I included HBV and HCV as an OI, but there this is subject to limitation because it would only count if it was a reactivation. Nevertheless, these infections were lower among the MS group, so the bias is towards the null. Third, due to large sample size limitations, I was unable to impute values for missing data. This may have been problematic for the MS group because MS patients only constituted 0.44% of the sample. Fourth, the data is collected for billing purposes and not for research. Thus, it is possible that not all MS or comorbidity diagnoses were captured if they were not considered an active problem and receiving treatment while hospitalized. Fifth, HCUP-NIS does not provide information medications or date since MS diagnosis. Thus, we could not evaluate susceptibility to infections based on type of disease modifying therapy or duration of illness. It has also been found in a recent large real-world cohort of multiple disease modifying therapies, that antibiotics are more commonly prescribed with anti-CD20 MS therapies ad antiherpetics are more commonly prescribed with fingolimod and natalizumab (Luna, 2019). If we would be very interesting to evaluate the relationship between prophylactic medications and risk of infection in this population. Sixth, the data is from 2018 and four new DMTs have been approved since then (siponimod, ozanimod, ofatumumab, ponesimod) which may impose different risks to OIs. Seventh, CDI was not included in the hospital OI definition because 20-27% are thought to be community acquired and there is no ICD-10 code to differentiate community from hospital acquired. The CDI risk was much higher among the MS group, so it is very likely that the secondary hospital OI endpoint is underestimated. Eighth, we use the term ‘risk’, but for the ‘any oi’ endpoint, we cannot confirm that these were new infections in 2018 and that the infection came after the MS diagnosis. Nine, with the GENMOD procedure, we were able to account for in-hospital correlations, but not the complex clustered sampling methodology.

Reflection:

This internship has been a great learning experience.

First, I had the opportunity to learn how to decrease selection bias through eligibility criteria (i.e. excluding people with a principal diagnosis of an infection) and deciding how to include covariates. The two pieces of advice from Dr. Singer that were especially helpful in this area were (1) our goal is not to perfectly predict OIs (2) a variable is only a confounder if it is related to both the exposure and the outcome.

Second, this was my first time working with complex sampling design data and utilizing procedures to accommodate that. I am very grateful that I learned about this because had I not, I may have submitted a paper for publication that I made false claims about the data representing the US population, when really the results only applied to my sample.

Third, this was my first time working with really big data and it was difficult to say the least. I learned that models must be much simpler when you have >7.5 million records and you might not be able to do things like propensity score matching, include lots of covariates, or covariates with many levels but relatively small observations. I also learned the importance of dropping any variable you are not actively using and to decrease the automatic variable length of 8 to 3 for all numeric variables.

Fourth, this project has really allowed me to appreciate the differences between R and SAS. I prefer R for creating a table 1 (took me a few hours every time I did it with SAS) and visualizations. However, R did not handle the big data well. SAS was great for handling the big data and the SAS documentation is much more efficient and detailed than R help forums. Furthermore, I am now proficient with using SAS on terminal, which is what I will have to for my fellowship.

Fifth, I am so happy that I learned about modified Poisson regression for calculating relative risks. I did not know that this was a possibility, and it is something that we did not learn in our categorical analysis class this summer. I am certain I will be using this in the future.

Lastly, I cannot believe how much work goes into a small paper. I will be much more mindful of how I critique other's work from now on. We really need to highlight the effort that authors put into the work and not just the limitations. I am certain that if this work is acceptable for publication that nobody will understand how much work went into determining what constitutes an OI, flagging 100s of diagnosis codes and then checking them and then finding out you messed something up, installing elixishauser comorbidity software, installing CCSR software (this took 13+ hours and I only used one variable from it), figuring out which models will run for less than

26 hours before crashing, changing the outcome, and changing the population multiple times (all adults, adults and excluding secondary oi, adults and excluding primary oi, adults excluding primary oi and other select infections).

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Appendix

ICD-10 Codes

Hospital acquired OIs were defined as an ICD-10 code for one of the following nosocomial condition (‘Y95), Ventilator associated pneumonia (‘J95851’), infection due to prosthetic urinary device (‘T835’), surgical infection(‘T814’), bloodstream infection due to central venous catheter (‘T8021).

Any OI was defined as the following: recurrent pneumonia (Z8701), invasive group B streptococci (B951), invasive enterobacteriaceae ('B965' 'B961' 'A413' 'A492' 'B963' 'A4151', 'A4152', 'A4153', 'A4159', 'B9620', 'B9629',' A4153'), disseminated tuberculosis ('B90', 'A17', 'A18', 'A19', 'A154'), invasive bacterial infection caused by staphylococcus aureus, listeria, pseudomonas aeruginosa, E.coli, klebsiella sp, Haemophilus influenzae, or Serratia ('A40', 'A41', 'B95', 'G00', 'R7881', 'A3211', 'A327'), disseminated bartonella ('A440'), legionella pulmonary infection ('A481), M. avium disseminated or extrapulmonary disease ('A312', 'A318', 'A319'), severe oropharyngeal candidiasis, esophagitis, candidiasis of trachea and bronchi, or invasive extrapulmonary candidiasis ('B3781', 'B371', 'B375', 'B376', 'B377'), invasive aspergillus (B440), pneumocystis pneumonia ('B59'), extrapulmonary cryptococcosis ('B451', 'B453', 'B457'), disseminated or extrapulmonary coccidioidomycosis ('B384','B387'), disseminated or extrapulmonary hisotplasmosis ('B393', 'B394', 'B399'), mucormycosis ('B464'), CMV pneumonia ('B250'), CMV pancreatitis ('B252'), CMV meningitis, other CMV complication, or CMV neuropathy ('B2712', 'B2719', 'B2711'), Epstein-Barr virus ('D823'), Herpesviral encephalitis ('B004'), systemic varicella ('B010', 'B012', 'B0111', 'B0112', 'B0189'), herpes zoster ('B02'), influenza ('J09', 'J10'), respiratory syncytial virus pneumonia ('J121'), Human metapneumovirus pneumonia ('J123'), Human herpesvirus 6 (HHV6) and Human herpesvirus 7 (HHV7) infections ('B10'), parvovirus ('B34'), Progressive multifocal leukoencephalopathy (PML) ('A812'), babesia ('B600'), toxoplasma gondii ('B58), Visceral leishmaniasis ('B550'), Acanthamoeba ('B6011'), Naegleriasis ('B602'), strongyloidiasis ('B787'), taenia ('B68'), nosocomial ('Y95), catheter infection ('T835'), surgical infection('T814'), bloodstream catheter infection ('T8021'), clostridium difficile ('A047').

S1 PROC SURVEYFREQ for unadjusted RRs and ORs

Hospital OI

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The SURVEYFREQ Procedure

Table of MS by sec_hosp_oi
Controlling for eligible=1 : eligible

MS	sec_hosp_oi	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent
0 : Control	0 : no hospital oi	5112409	25562039	234826	99.0531	0.0091
	1 : hospital oi	25835	129175	2273	0.5006	0.0073
	Total	5138244	25691214	236107	99.5537	0.0045
1 : MS	0 : no hospital oi	22822	114110	1642	0.4422	0.0045
	1 : hospital oi	214	1070	72.00329	0.0041	0.0003
	Total	23036	115180	1650	0.4463	0.0045
Total	0 : no hospital oi	5135231	25676149	235998	99.4953	0.0073
	1 : hospital oi	26049	130245	2285	0.5047	0.0073
	Total	5161280	25806394	237286	100.0000	

Any OI

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The SURVEYFREQ Procedure

Data Summary

Number of Strata	205
Number of Clusters	4550
Number of Observations	7105498
Sum of Weights	35527481

Table of MS by oi
Controlling for eligible=1 : eligible

MS	oi	Frequency	Weighted Frequency	Std Err of Wgt Freq	Percent	Std Err of Percent
0 : Control	0 : no any oi	4754305	23771520	218193	92.1148	0.0492
	1 : any oi	383939	1919695	22096	7.4388	0.0482
	Total	5138244	25691214	236107	99.5537	0.0045
1 : MS	0 : no any oi	20263	101315	1480	0.3926	0.0041
	1 : any oi	2773	13865	325.61947	0.0537	0.0011
	Total	23036	115180	1650	0.4463	0.0045
Total	0 : no any oi	4774568	23872835	219230	92.5074	0.0485
	1 : any oi	386712	1933560	22255	7.4926	0.0485
	Total	5161280	25806394	237286	100.0000	

Rao-Scott Chi-Square Test

Pearson Chi-Square	689.6566
Design Correction	1.0495
Rao-Scott Chi-Square	657.1557
DF	1
Pr > ChiSq	<.0001
F Value	657.1557
Num DF	1
Den DF	4345
Pr > F	<.0001

S2 PROC GENMOD for Relative Risks

Hospital OI

The GENMOD Procedure

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept		-6.4769	0.0917	-6.6565	-6.2973	-70.67	<.0001
MS	1	0.6458	0.0680	0.5126	0.7790	9.50	<.0001
age_c	2	0.8209	0.0387	0.7450	0.8969	21.19	<.0001
age_c	3	1.2840	0.0380	1.2096	1.3584	33.83	<.0001
age_c	4	1.3683	0.0414	1.2870	1.4495	33.01	<.0001
age_c	5	1.5095	0.0448	1.4217	1.5972	33.70	<.0001
FEMALE	1	-0.3141	0.0137	-0.3409	-0.2873	-22.98	<.0001
race	2	-0.0663	0.0244	-0.1140	-0.0185	-2.72	0.0065
race	3	-0.1857	0.0330	-0.2504	-0.1210	-5.62	<.0001
race	7	-0.1225	0.0407	-0.2022	-0.0428	-3.01	0.0026
pay1	2	-0.1002	0.0278	-0.1546	-0.0458	-3.61	0.0003
pay1	3	-0.3227	0.0247	-0.3711	-0.2744	-13.08	<.0001
pay1	7	-0.3312	0.0367	-0.4031	-0.2593	-9.03	<.0001
PL_NCHS	2	-0.0301	0.0314	-0.0917	0.0315	-0.96	0.3383
PL_NCHS	3	0.0601	0.0365	-0.0114	0.1316	1.65	0.0993
PL_NCHS	4	0.0907	0.0417	0.0090	0.1724	2.18	0.0296
PL_NCHS	5	0.1625	0.0405	0.0831	0.2419	4.01	<.0001
PL_NCHS	6	0.1780	0.0423	0.0950	0.2610	4.21	<.0001
HOSP_REGION	2	0.2039	0.0481	0.1097	0.2982	4.24	<.0001
HOSP_REGION	3	0.2424	0.0473	0.1498	0.3350	5.13	<.0001
HOSP_REGION	4	0.1509	0.0481	0.0565	0.2452	3.13	0.0017
ZIPINC_QRTL	2	-0.0414	0.0221	-0.0846	0.0018	-1.88	0.0606
ZIPINC_QRTL	3	-0.0510	0.0252	-0.1005	-0.0016	-2.02	0.0432
ZIPINC_QRTL	4	-0.1157	0.0289	-0.1723	-0.0591	-4.01	<.0001
ELECTIVE	1	-0.5297	0.0289	-0.5864	-0.4731	-18.33	<.0001
ED_record	1	0.0524	0.0253	0.0027	0.1021	2.07	0.0387
HOSP_LOCTEACH	2	0.0456	0.0601	-0.0722	0.1635	0.76	0.4479
HOSP_LOCTEACH	3	0.2242	0.0554	0.1157	0.3328	4.05	<.0001
H_CONTRL	2	0.0189	0.0456	-0.0706	0.1083	0.41	0.6791
H_CONTRL	3	-0.2415	0.0557	-0.3506	-0.1324	-4.34	<.0001
HOSP_BEDSIZE	2	0.0617	0.0359	-0.0087	0.1322	1.72	0.0858
HOSP_BEDSIZE	3	0.1268	0.0337	0.0607	0.1928	3.76	0.0002
diab	1	0.1585	0.0150	0.1291	0.1879	10.56	<.0001
htn	1	-0.1259	0.0170	-0.1593	-0.0926	-7.39	<.0001
DEPRESS	1	0.1570	0.0189	0.1201	0.1940	8.33	<.0001
OBESE	1	0.1209	0.0178	0.0859	0.1558	6.78	<.0001
tobacco	1	-0.1411	0.0209	-0.1820	-0.1002	-6.76	<.0001

Contrast Estimate Results

Label	Mean Estimate	Mean Confidence Limits		L'Beta Estimate	Standard Error	Alpha	L'Beta Confidence Limits		Chi-Square	Pr > ChiSq
RR MS vs. no MS	1.9076	1.6697	2.1794	0.6458	0.0680	0.05	0.5126	0.7790	90.29	<.0001
Exp(RR MS vs. no MS)				1.9076	0.1297	0.05	1.6697	2.1794		

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The GENMOD Procedure

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept		-3.3866	0.0401	-3.4652	-3.3079	-84.38	<.0001
MS	1	0.4241	0.0188	0.3873	0.4609	22.59	<.0001
age_c	2	0.5080	0.0105	0.4874	0.5286	48.32	<.0001
age_c	3	0.7702	0.0123	0.7460	0.7944	62.39	<.0001
age_c	4	0.7824	0.0141	0.7547	0.8101	55.43	<.0001
age_c	5	0.9047	0.0156	0.8741	0.9354	57.87	<.0001
FEMALE	1	0.0290	0.0047	0.0198	0.0382	6.19	<.0001
race	2	-0.0965	0.0081	-0.1124	-0.0806	-11.90	<.0001
race	3	-0.0378	0.0113	-0.0599	-0.0157	-3.35	0.0008
race	7	-0.0137	0.0198	-0.0526	0.0251	-0.69	0.4885
pay1	2	-0.0723	0.0087	-0.0894	-0.0552	-8.26	<.0001
pay1	3	-0.2692	0.0078	-0.2844	-0.2539	-34.62	<.0001
pay1	7	-0.1956	0.0106	-0.2163	-0.1749	-18.51	<.0001
PL_NCHS	2	0.0011	0.0124	-0.0232	0.0254	0.09	0.9279
PL_NCHS	3	0.0094	0.0146	-0.0191	0.0380	0.65	0.5180
PL_NCHS	4	0.0154	0.0155	-0.0149	0.0457	1.00	0.3182
PL_NCHS	5	0.0663	0.0154	0.0361	0.0964	4.30	<.0001
PL_NCHS	6	0.0647	0.0166	0.0321	0.0972	3.89	<.0001
HOSP_REGION	2	0.1067	0.0223	0.0630	0.1504	4.79	<.0001
HOSP_REGION	3	0.1574	0.0214	0.1155	0.1994	7.35	<.0001
HOSP_REGION	4	0.1207	0.0229	0.0759	0.1656	5.28	<.0001
ZIPINC_QRTL	2	-0.0075	0.0067	-0.0207	0.0057	-1.12	0.2641
ZIPINC_QRTL	3	-0.0177	0.0081	-0.0336	-0.0019	-2.19	0.0285
ZIPINC_QRTL	4	-0.0150	0.0103	-0.0351	0.0051	-1.46	0.1438
ELECTIVE	1	-0.7236	0.0161	-0.7551	-0.6920	-44.91	<.0001
ED_record	1	0.1055	0.0134	0.0792	0.1318	7.87	<.0001
HOSP_LOCTEACH	2	0.0102	0.0197	-0.0284	0.0488	0.52	0.6048
HOSP_LOCTEACH	3	0.0718	0.0192	0.0342	0.1094	3.74	0.0002
H_CONTRL	2	-0.0419	0.0261	-0.0930	0.0091	-1.61	0.1076
H_CONTRL	3	-0.1812	0.0271	-0.2343	-0.1280	-6.68	<.0001
HOSP_BEDSIZE	2	0.0222	0.0138	-0.0049	0.0494	1.61	0.1083
HOSP_BEDSIZE	3	0.0834	0.0147	0.0546	0.1122	5.68	<.0001
diab	1	0.2106	0.0049	0.2011	0.2201	43.30	<.0001
htn	1	0.0762	0.0058	0.0648	0.0875	13.17	<.0001
DEPRESS	1	0.1438	0.0056	0.1327	0.1548	25.47	<.0001
OBESE	1	0.0541	0.0060	0.0423	0.0659	9.01	<.0001
tobacco	1	-0.1000	0.0066	-0.1130	-0.0871	-15.13	<.0001

Contrast Estimate Results

Label	Mean Estimate	Mean Confidence Limits		L'Beta Estimate	Standard Error	Alpha	L'Beta Confidence Limits		Chi-Square	Pr > ChiSq
RR MS vs. no MS	1.5282	1.4730	1.5855	0.4241	0.0188	0.05	0.3873	0.4609	510.40	<.0001
Exp(RR MS vs. no MS)				1.5282	0.0287	0.05	1.4730	1.5855		

Proc SurveyLogistic OR for hospital OI

The SURVEYLOGISTIC Procedure

Domain Analysis for domain eligible=1

Domain Summary

Number of Observations	7105498
Number of Observations in Domain	5161280
Number of Observations not in Domain	1944218
Sum of Weights in Domain	25806394

Model Information

Data Set	NIS.JULY_POP_TOTAL	
Response Variable	sec_hosp_oi	
Number of Response Levels	2	
Stratum Variable	NIS_STRATUM	NIS hospital stratum
Number of Strata	205	
Cluster Variable	HOSP_NIS	NIS hospital number
Number of Clusters	4391	
Weight Variable	DISCWT	NIS discharge weight
Model	Binary Logit	
Optimization Technique	Fisher's Scoring	
Variance Adjustment	Degrees of Freedom (DF)	

Variance Estimation

Method	Taylor Series
Variance Adjustment	Degrees of Freedom (DF)

Number of Observations Read	7105498
Number of Observations Used	6735633
Sum of Weights Read	25806394
Sum of Weights Used	24637106

Response Profile

Ordered Value	sec_hosp_oi	Total Frequency	Total Weight
1	0	4902517	24512581
2	1	24905	124525

Probability modeled is sec_hosp_oi=0.

NOTE: 369865 observations were deleted due to missing values for the response or explanatory variables.

Class Level Information

Class	Value	Design Variables
MS	0	1
	1	-1

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	1565273.8	1515041.6
SC	1565288.8	1515597.3
-2 Log L	1565271.8	1514967.6

Testing Global Null Hypothesis: BETA=0

Test	F Value	Num DF	Den DF	Pr > F
Likelihood Ratio	121.16	24.1943	101277	<.0001
Score	142.54	36	4151	<.0001
Wald	170.54	36	4151	<.0001

NOTE: Second-order Rao-Scott design correction
0.4880 applied to the Likelihood Ratio test.

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The SURVEYLOGISTIC Procedure

Domain Analysis for domain eligible=1

Type 3 Analysis of Effects

Effect	F Value	Num DF	Den DF	Pr > F
MS	89.83	1	4186	<.0001
age_c	338.78	4	4183	<.0001
FEMALE	533.94	1	4186	<.0001
race	12.83	3	4184	<.0001
pay1	71.86	3	4184	<.0001
PL_NCHS	6.61	5	4182	<.0001
HOSP_REGION	9.25	3	4184	<.0001
ZIPINC_QRTL	5.47	3	4184	0.0009
ELECTIVE	340.17	1	4186	<.0001
ED_record	4.28	1	4186	0.0387
HOSP_LOCTEACH	17.72	2	4185	<.0001
H_CONTRL	19.64	2	4185	<.0001
HOSP_BEDSIZE	7.19	2	4185	0.0008
diab	114.31	1	4186	<.0001
htn	55.35	1	4186	<.0001
DEPRESS	70.29	1	4186	<.0001
OBESE	46.90	1	4186	<.0001
tobacco	46.50	1	4186	<.0001

Effect		Point Estimate	95% Confidence Limits	
MS	0 vs 1	1.918	1.677	2.195
age_c	1 vs 7	59.830	45.686	78.354
age_c	2 vs 7	26.293	20.514	33.701
age_c	3 vs 7	16.511	13.072	20.854
age_c	4 vs 7	15.168	12.222	18.823
FEMALE	0 vs 1	0.729	0.710	0.749
race	1 vs 7	0.884	0.816	0.958
race	2 vs 7	0.945	0.865	1.032
race	3 vs 7	1.066	0.968	1.173
pay1	1 vs 7	0.716	0.667	0.770
pay1	2 vs 7	0.793	0.735	0.855
pay1	3 vs 7	0.991	0.922	1.066
PL_NCHS	1 vs 6	1.196	1.100	1.301
PL_NCHS	2 vs 6	1.233	1.134	1.342
PL_NCHS	3 vs 6	1.126	1.038	1.222
PL_NCHS	4 vs 6	1.092	1.005	1.187

NOTE: The degrees of freedom in computing the confidence limits is 4186.

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The SURVEYLOGISTIC Procedure

Domain Analysis for domain eligible=1

Odds Ratio Estimates

Effect		Point Estimate	95% Confidence Limits	
PL_NCHS	5 vs 6	1.016	0.936	1.103
HOSP_REGION	1 vs 4	1.164	1.058	1.281
HOSP_REGION	2 vs 4	0.948	0.877	1.024
HOSP_REGION	3 vs 4	0.912	0.848	0.980
ZIPINC_QRTL	1 vs 4	0.890	0.841	0.942
ZIPINC_QRTL	2 vs 4	0.928	0.882	0.976
ZIPINC_QRTL	3 vs 4	0.937	0.893	0.983
ELECTIVE	0 vs 1	0.587	0.555	0.621
ED_record	0 vs 1	1.054	1.003	1.108
HOSP_LOCTEACH	1 vs 3	1.253	1.122	1.400
HOSP_LOCTEACH	2 vs 3	1.197	1.115	1.285
H_CONTRL	1 vs 3	0.784	0.704	0.874
H_CONTRL	2 vs 3	0.769	0.708	0.836
HOSP_BEDSIZE	1 vs 3	1.136	1.063	1.214
HOSP_BEDSIZE	2 vs 3	1.068	0.999	1.140
diab	0 vs 1	1.173	1.139	1.208
htn	0 vs 1	0.881	0.852	0.911
DEPRESS	0 vs 1	1.171	1.129	1.215
OBESE	0 vs 1	1.129	1.091	1.170
tobacco	0 vs 1	0.867	0.833	0.904

NOTE: The degrees of freedom in computing the confidence limits is 4186.

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The SURVEYLOGISTIC Procedure

Domain Analysis for domain eligible=1

Type 3 Analysis of Effects

Effect	F Value	Num DF	Den DF	Pr > F
MS	485.51	1	4186	<.0001
age_c	1121.51	4	4183	<.0001
FEMALE	45.61	1	4186	<.0001
race	48.98	3	4184	<.0001
pay1	463.48	3	4184	<.0001
PL_NCHS	6.91	5	4182	<.0001
HOSP_REGION	18.98	3	4184	<.0001
ZIPINC_QRTL	1.59	3	4184	0.1901
ELECTIVE	2108.62	1	4186	<.0001
ED_record	67.30	1	4186	<.0001
HOSP_LOCTEACH	14.32	2	4185	<.0001
H_CONTRL	53.18	2	4185	<.0001
HOSP_BEDSIZE	17.51	2	4185	<.0001
diab	1992.84	1	4186	<.0001
htn	177.00	1	4186	<.0001
DEPRESS	631.30	1	4186	<.0001
OBESE	82.17	1	4186	<.0001
tobacco	240.13	1	4186	<.0001

NOTE: The following parameters have been set to 0, since the variables are a linear combination of other variables as shown.

The SURVEYLOGISTIC Procedure

Domain Analysis for domain eligible=1

Analysis of Maximum Likelihood Estimates

Parameter		Estimate	Standard Error	t Value	Pr > |t|
PL_NCHS	4	0.0118	0.0105	1.13	0.2583
PL_NCHS	5	-0.0443	0.00991	-4.48	<.0001
HOSP_REGION	1	0.1061	0.0160	6.63	<.0001
HOSP_REGION	2	-0.0116	0.0127	-0.91	0.3606
HOSP_REGION	3	-0.0676	0.0112	-6.04	<.0001
ZIPINC_QRTL	1	-0.0111	0.00585	-1.89	0.0583
ZIPINC_QRTL	2	-0.00272	0.00488	-0.56	0.5775
ZIPINC_QRTL	3	0.00848	0.00463	1.83	0.0673
ELECTIVE	0	-0.3858	0.00840	-45.92	<.0001
ED_record	0	0.0586	0.00714	8.20	<.0001
HOSP_LOCTEACH	1	0.0301	0.0135	2.22	0.0264
HOSP_LOCTEACH	2	0.0188	0.00999	1.89	0.0594
H_CONTRL	1	-0.0819	0.0182	-4.50	<.0001
H_CONTRL	2	-0.0357	0.0119	-3.00	0.0027
HOSP_BEDSIZE	1	0.0388	0.00893	4.35	<.0001
HOSP_BEDSIZE	2	0.0143	0.00863	1.66	0.0968
diab	0	0.1174	0.00263	44.64	<.0001
htn	0	0.0415	0.00312	13.30	<.0001
DEPRESS	0	0.0800	0.00318	25.13	<.0001
OBESE	0	0.0297	0.00328	9.06	<.0001
tobacco	0	-0.0552	0.00356	-15.50	<.0001

NOTE: The degrees of freedom for the t tests is 4186.

Odds Ratio Estimates

Effect		Point Estimate	95% Confidence Limits	
MS	0 vs 1	1.613	1.546	1.683
age_c	1 vs 7	14.137	12.783	15.635
age_c	2 vs 7	8.338	7.586	9.165
age_c	3 vs 7	6.286	5.754	6.866
age_c	4 vs 7	6.201	5.719	6.724
FEMALE	0 vs 1	1.034	1.024	1.044
race	1 vs 7	0.985	0.944	1.028
race	2 vs 7	1.096	1.048	1.146
race	3 vs 7	1.027	0.982	1.074
pay1	1 vs 7	0.806	0.788	0.824
pay1	2 vs 7	0.875	0.853	0.897
pay1	3 vs 7	1.081	1.055	1.107
PL_NCHS	1 vs 6	1.074	1.036	1.113
PL_NCHS	2 vs 6	1.073	1.036	1.110
PL_NCHS	3 vs 6	1.063	1.027	1.099
PL_NCHS	4 vs 6	1.056	1.025	1.087

NOTE: The degrees of freedom in computing the confidence limits is 4186.

the confidence limits is 4186.

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The SURVEYLOGISTIC Procedure

Domain Analysis for domain eligible=1

Odds Ratio Estimates

Effect		Point Estimate	95% Confidence Limits	
PL_NCHS	5 vs 6	0.998	0.970	1.027
HOSP_REGION	1 vs 4	1.142	1.088	1.199
HOSP_REGION	2 vs 4	1.015	0.976	1.057
HOSP_REGION	3 vs 4	0.960	0.927	0.995
ZIPINC_QRTL	1 vs 4	0.984	0.962	1.006
ZIPINC_QRTL	2 vs 4	0.992	0.972	1.013
ZIPINC_QRTL	3 vs 4	1.003	0.986	1.020
ELECTIVE	0 vs 1	0.462	0.447	0.478
ED_record	0 vs 1	1.124	1.093	1.156
HOSP_LOCTEACH	1 vs 3	1.082	1.038	1.128
HOSP_LOCTEACH	2 vs 3	1.070	1.041	1.100
H_CONTRL	1 vs 3	0.819	0.774	0.867
H_CONTRL	2 vs 3	0.858	0.831	0.886
HOSP_BEDSIZE	1 vs 3	1.096	1.062	1.131
HOSP_BEDSIZE	2 vs 3	1.070	1.038	1.103
diab	0 vs 1	1.265	1.252	1.278
htn	0 vs 1	1.086	1.073	1.100
DEPRESS	0 vs 1	1.173	1.159	1.188
OBESE	0 vs 1	1.061	1.048	1.075
tobacco	0 vs 1	0.895	0.883	0.908

NOTE: The degrees of freedom in computing the confidence limits is 4186.

Association of Predicted Probabilities and Observed Responses

Percent Concordant	65.0	Somers' D	0.313
Percent Discordant	33.6	Gamma	0.318
Percent Tied	1.4	Tau-a	0.043
Pairs	1.6842066E12	c	0.657