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Identification of Stevens–Johnson syndrome and toxic epidermal necrolysis in electronic health record databases†

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Abstract

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

This study was approved by each participating site's institutional review board.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

Background—Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) carry a high mortality risk. While identifying clinical and genetic risk factors for these conditions has been hindered by their rarity, large electronic health databases hold promise for identifying large numbers of cases for study, especially with the introduction in 2008 of ICD-9 codes more specific for these conditions.

Objective—The objective of this study is to estimate the validity of ICD-9 codes for ascertaining SJS/TEN in 12 collaborating research units in the USA, covering almost 60 million lives.

Methods—From the electronic databases at each site, we ascertained potential cases of SJS/TEN using ICD-9 codes. At five sites, a subset of medical records was abstracted and standardized criteria applied by board-certified dermatologists to adjudicate diagnoses. Multivariate logistic regression was used to identify factors independently associated with validated SJS/TEN cases.

Results—A total of 56 591 potential cases of SJS/TEN were identified. A subset of 276 charts was selected for adjudication and 39 (of the 276) were confirmed as SJS/TEN. Patients with the ICD-9 codes introduced after 2008 were more likely to be confirmed as cases (OR 3.32; 95%CI 0.82, 13.47) than those identified in earlier years. Likelihood of case status increased with length of hospitalization. Applying the probability of case status to the 56 591 potential cases, we estimated 475–875 to be valid SJS/TEN cases.

Conclusion—Newer ICD-9 codes, along with length of hospitalization, identified patients with a high likelihood of SJS/TEN. This is important for identification of subjects for future pharmacogenomics studies.

CAPSULE SUMMARY

The combination of newly introduced ICD-9 codes, along with length of hospitalization, strongly predicts SJS/TEN case status. This information could be critical for studies interested in identifying large numbers of cases for pharmacogenomic study.

Keywords

Stevens–Johnson syndrome; toxic epidermal necrolysis; pharmacoepidemiology

INTRODUCTION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions with a high risk of death. SJS has a mortality rate of approximately 5%, while TEN has a mortality rate of 25–35%. Both have been associated with exposure to certain types of medications and medication classes including antibiotics, antiepileptics, allopurinol, and non-steroidal anti-inflammatory agents.^{1,2} Other conditions associated with SJS and TEN include HIV infection, herpes, *Mycoplasma pneumoniae*, radiotherapy, lupus erythematosus, and collagen vascular disease. While studies of clinical and genetic risk factors for severe cutaneous adverse reactions to drugs have been limited by their rarity, large electronic databases hold promise for identifying large numbers of SJS and TEN patients for such studies.

Carbamazepine is the most common identifiable cause of SJS and TEN in Southeast Asian countries.³ Carbamazepine-associated SJS-TEN is strongly associated with the HLA-B*1502 allele in Han Chinese and in persons from Malaysia, Thailand, India, and Hong Kong.⁴⁻⁹ The HLA-A*3101 allele has been associated with carbamazepine-associated hypersensitivity reactions, and more recently, with SJS-TEN in persons of Japanese and of European descent.^{10,11} Screening Taiwanese patients for the presence of HLA-B*1502 allele prior to initiating carbamazepine reduces the incidence of SJS-TEN, showing the promise of this type of personalized therapeutics approach.¹² Locharenkul has called for HLA-B*1502 screening before prescribing carbamazepine, particularly in those ethnic groups (eastern China, Taiwan, Thailand and Malaysia) showing strong association between the biomarker and risk for SJS/TEN.¹³

Much remains to be learned about additional genetic variants that may interact with drugs to increase the risk for SJS and/or TEN. The task of identifying SJS and TEN cases from electronic health record or claims data has been hindered by the low specificity of the ICD-9 diagnosis codes used for SJS or TEN. Until recently, the code most commonly used for SJS and TEN was also used to code for erythema multiforme major and minor, as well as for Staphylococcal scalded skin syndrome. In October 2008, the ICD-9 codes 695.13, 695.14, and 695.15 were introduced and intended to be specific for SJS, TEN, and SJS/TEN overlap syndrome. However, their large-scale use in electronic data sources has yet to be evaluated. A systematic review of methods for evaluating these conditions found that studies of validated algorithms to identify SJS and TEN were based on data 25 years old and did not assess the October 2008 coding changes.¹⁴

In this study, we evaluated the feasibility of performing large-scale, population-based studies of SJS and TEN in 12 collaborating managed care organizations and health benefits company research units in the USA, covering a combined population of almost 60 million lives. Our goals were to evaluate the specificity and predictive values of ICD-9 codes in use prior to and after October 2008, to develop a predictive model for SJS and TEN based on one or more clinical or demographic variables and/or ICD-9 codes, and then to estimate the total number of SJS and TEN cases potentially available for a population-based pharmacogenetic study of SJS and TEN, with a focus on the number available following exposure to antiepileptic drugs (AEDs).

METHODS

Study population

This study was performed in 11 HMO Research Network (HMORN) sites including Kaiser Permanente, Geisinger Health System, Group Health Research Institute, Harvard Pilgrim Health Care, HealthPartners Institute, Henry Ford Hospital, and Marshfield Clinic Research Foundation, and in HealthCore, Inc. Potential adult and pediatric cases of SJS/TEN were identified from 1/1/2001 through 30/4/2012 at nine HMORN sites and from 1/1/2001 through 31/12/ 2011 at two HMORN sites and HealthCore, Inc. This study was approved by each participating site's institutional review board.

Data sources and characteristics

The HMORN health plans provide comprehensive treatment services to defined populations and track member's care and outcomes through multiple electronic databases and disease registries. Unique member identifiers are used to track members across databases covering enrollment periods and resource utilization. Clinical data are available for inpatient and outpatient diagnoses and procedures, pharmacy data, and lab testing and results. Nearly all sites have 90% of members with pharmacy benefits.

HealthCore Inc. is an independent research-focused subsidiary of WellPoint, Inc., and its research data encompass longitudinally integrated medical and pharmacy claims, enrollment, and electronic outpatient laboratory results on approximately 48 million members. Both HealthCore and the HMORN sites augment data from their automated electronic sources with inpatient and outpatient medical record review.

Study approach

We identified potential cases of SJS and TEN and classified them into three groups. Group 1 consisted of patients who received an inpatient ICD-9 code of 695.1x between 1/1/2001–31/12/2008. Limiting this group to the inpatient setting was carried out to make our results more comparable with past published data on the performance of codes used for SJS and TEN. Group 2 included patients with a diagnosis in the emergency department, outpatient clinic setting, or inpatient setting of ICD-9 codes 695.12–695.15 between 1/8/2008 and 30/4/2012 (31/12/2012 in the case of Harvard Pilgrim, HealthCore, and HealthPartners). Group 3 included patients with inpatient ICD-9 codes 279.5, 279.51, 279.53, 695.8, 695.81, 693.0x, 694.8x, or 694.4x, or diagnosis codes 692.9, E85x.x-E858.9, 693.8, 692.89, 695.89, 695.1x, 692.3x, or 695.0 used in an inpatient setting plus exposure to antiepileptics, select antibiotics (primarily sulfonamides, penicillins, cephalosporins, and antivirals), or anti-gout medications in the 60 days before inpatient admission, in the period 1/1/2001–30/4/2012 (31/12/2011 for three sites as noted previously). In general, Group 1 used “old” codes prior to October 2008, Group 2 used “new” codes released after October 2008, and Group 3 used codes assumed to be less specific than those used in Group 1 or 2. The patients selected into these three groups comprised the total study population. For clarity, in the remainder of the manuscript, Groups 1, 2, and 3 are referred to as “old codes”, “new codes”, and “non-specific codes”, respectively.

From this group of potential cases, at five sites (due to chart availability and funding constraints), a sample of 277 patients was selected for medical record review and abstraction using standardized case report forms. Patient characteristics including demographics, current medical illness (including description of skin rash and laboratory values), medical history (including exposure to prescription drugs and past hospitalizations), and history of drug allergy and adverse drug reactions were abstracted and supplemented with electronic medical data (a list of the study variables collected and assessed is shown in Supporting Information Appendices 1 and 2). The 277 cases were selected for review according to the following strategy: 103 were randomly selected from patients with at least one inpatient ICD-9 code 695.1; 51 from patients with at least one inpatient ICD-9 listed in the non-specific codes group during the period before 1/10/08; 51 from the group of patients with at

least one inpatient ICD-9 code listed in the non-specific codes group but restricted to the period after 1/10/08; 11 patients with an inpatient ICD-9 code 695.1 restricted to the period after 1/10/08; 45 patients with inpatient code 695.12 (new code group); and 16 randomly selected patients with ICD-9 codes 695.13, 695.14, or 695.15 (new code group). This approach was chosen to enable sampling a number of patients with non-specific codes before and after 2008, as well as patients with more specific codes after 2008 to evaluate how these codes performed to identify SJS/TEN. The expectation was that there would be many more patients with non-specific codes, so the aforementioned numbers led to sampling approximately equal numbers from each group.

Case criteria and adjudication process

Three board-certified dermatologists were assigned to review equal numbers of abstracted cases. For each case, two dermatologists (blinded to the patient's discharge diagnoses) reviewed the abstracted data. If there was disagreement, a third dermatologist performed a blinded record review and provided the tie-breaking vote.

The outcomes of interest were erythema multiforme major, SJS, TEN, and SJS/TEN overlap syndrome. The criteria necessary for case classification were as follows: (i) erythema multiforme major: hospitalization, skin findings described as target or raised, edematous papules distributed acraly with involvement of one or more mucous membranes, and epidermal detachment involves less than 10% of the total body surface area (TBSA); (ii) SJS: widespread blisters predominant on the trunk and face, presenting with erythematous or pruritic macules and one or more mucous membrane erosions and epidermal detachment less than 10% TBSA; and (iii) TEN: same as for SJS except for epidermal detachment of at least 30% of TBSA. Where TBSA was not implicitly stated, cases were coded as SJS/TEN overlap. Supportive criteria included hospitalization, the presence of acute skin tenderness and pain, acute fulminant course, fever of greater than 38 °C, and diagnosis being made by a dermatologist and/or supported by a skin biopsy (when available).

The initial adjudication classified cases as definite, probable, possible, unlikely, or not a case. For the final analyses, cases were collapsed into a binary category as either confirmed (which included those adjudicated as definite, probable, or possible) or not confirmed (which included those adjudicated as unlikely or not a case). By unanimous decision after discussion among the dermatologists, it was felt that the chart review data were not adequate to conclusively distinguish between erythema multiforme major, SJS, TEN, and SJS/TEN overlap. Therefore, these categories were combined and considered as a single composite outcome in all the analyses and are referred to in this manuscript as SJS/TEN.

Medication exposure ascertainment and other covariates of interest

Electronic pharmacy files were used to identify patient medication use that preceded the onset of SJS or TEN.

Analytic approach

Using the 276 patients that were reviewed for validated case status (one patient out of the original 277 was found ineligible for inclusion and dropped from analyses), bivariate

analyses were performed on demographic and predictor variables, and odds ratios (OR), confidence, and p -values were calculated. Positive predictive values (PPVs) were calculated for each of the three groups as well. Multivariate logistic regression was then used to identify demographic and clinical variables independently associated with validated SJS/TEN (Table 1). For this step, the adjudicated sample of 276 patients was modeled using logistic regression with stepwise selection. Model entry criteria was set at $p = 0.15$; exit criteria was set at $p = 0.10$. We did not create separate models stratified by group, as this was not feasible because of the relatively small numbers in each group.

The final model was developed and applied to the study population so that a case probability was calculated for each of the 56 591 members. By applying the strata-specific probabilities to the number of potential cases of SJS/TEN for each strata formed by the combination of variables in the final model, we summed the strata-specific estimates, which then represented the final number of potential cases in the full study population.

Finally, because one of the primary study purposes was to evaluate using administrative medical records for identifying patients with SJS/TEN following AED use, we carried out a sensitivity analysis, and repeated the multivariate logistic regression modeling described earlier but limited to patients with AED exposure in the 60 days prior to the index date.

All analyses were carried out in SAS 9.2 for Windows.

RESULTS

There were 56 591 persons across all sites who met the criteria to be included in groups 1, 2, or 3, based on the ICD-9 codes listed previously. Of these, 3143 were in group 1 (“old codes”), 1836 were in group 2 (“new codes”), and 51 972 were in group 3 (“non-specific codes”); people could be represented in more than one group. The demographic and clinical characteristics of the groups are shown in Table 2. Confirmed cases of SJS and TEN were predominantly female (59%), of Caucasian race (49%), and under or equal to 45 years of age (56%). Between 43–44% and 13–16% had been exposed to antibiotics or AEDs, respectively, in the 60 days preceding diagnosis. Despite the high antimicrobial use rate, few patients had a documented viral (5–7%), bacterial (3–4%), or fungal (3–4%) infection in the 60 days prior to diagnosis. Two patients (in the “new codes” group) had received antiretroviral agents in the 60 days prior to SJS/TEN diagnosis.

Medical record abstraction results

A total of 276 chart reviews were performed. All charts were adjudicated by two of three dermatologists, and the overall agreement between the dermatologists was 92% (kappa = 72%; Table 3). A third dermatologist was used to adjudicate 22 cases where the first two dermatologists rendered different case assignments.

Of the 276 reviewed cases, 39 were confirmed as cases of SJS/TEN, while 237 were judged not to be valid cases of SJS/TEN. Of the 39 cases, 25 originated from the old codes group, 12 were from the new codes group, and 2 were from the non-specific codes group (Table 3). The overall confirmation rates for the old codes group and the non-specific codes group

were 27% (25 of 94) and 2% (2 of 124), respectively. In the new codes group (the only group that included non-hospitalized patients), the confirmation rate was 21%. When stratified by hospitalization status, the confirmation rate in the new codes group was 50% for hospitalized cases, and 15% for non-hospitalized patients, respectively.

Prediction models

In the multivariate logistic regression models, patient group and length of hospital stay (LOS) were the only two risk factors independently associated with case status. Compared with patients with old codes, patients with new codes were more likely to be valid cases (OR 3.32; 95%CI 0.82, 13.47), while patients with the non-specific codes were less likely to be valid cases (OR 0.02; 95%CI 0.00, 0.11). Compared with patients not hospitalized, likelihood of case status increased with LOS (OR 1.66; 95%CI 0.25, 10.9 for 2 or fewer days, OR 1.78; 95%CI 1.60–38.28 for 3–5 days; OR 7.67, 95%CI 1.42,41.56 for 6–13 days, and OR 63.9; 95% CI 8.2, 499.1 for 14 days).

Table 4 shows the modeled probability (derived from the logistic regression model in the sample of patients selected for validation ($n = 276$)) of case status for all patients. There were four strata with validation probabilities of 50%, including the new codes group 2 with LOS 3–5 days; with LOS 6–13 days; with LOS of 14 or more days, and the old codes group 1 with LOS of 14 or more days. Applying these probabilities to the study population, in these four strata with validation probabilities of 50%, there were a total number of 1225 patients, within which there were an estimated 857 valid cases (see footnote, Table 4). Because this estimate is based on the application of the logistic regression model results to the original dataset, it likely has some degree of over-fitting and overestimation of the number of cases. We performed a sensitivity analysis using the lower 95% confidence limit of the modeled probability to each of the strata. Using this approach, the number of estimated valid cases decreased from 857 to 475.

As one of the main purposes of the study was to evaluate the possibility of using administrative medical records to efficiently identify patients with SJS/TEN following AED use, we repeated the multivariate logistic regression modeling but limited to patients in any of the three groups with prior AED exposure. It is important to note that these analyses were limited by the low number of cases: 43 of the 276 cases selected for validation were exposed to AEDs, and nine of these 43 were confirmed as SJS/TEN. In this model, only receipt of steroids was associated with validated case status. Patients receiving steroids were 7.3 times more likely to be validated as cases (OR 7.3; 95%CI 1.4, 36.7). Applying these results to the population of members with prior recent AED exposure and using only the lower estimate of the modeled probability, there were an estimated 52 cases among 189 AED exposed subjects in the old codes Group 1, 15 cases among 123 exposed subjects in the new codes Group 2, and 142 cases among 2243 exposed subjects in the non-specific codes Group 3.

DISCUSSION

We found that a combination of ICD-9 codes, along with LOS, identified a large group of patients with a high likelihood of having SJS/TEN. There was a large number of potential SJS/TEN cases ($n = 857$) predicted in the four strata with the highest modeled probabilities.

The PPV of the new ICD-9 codes 695.12–695.15 introduced in October 2008 was 21% but increased to 50% when we limited these codes to hospitalized cases—however, this is based on a relatively small number of cases. We also found that when used for patients hospitalized for three or more days, the PPV of these codes ranged from 57% to 92%. While our study suggests that case finding could be carried out efficiently using a small combination of codes, validation of case status via chart review will likely be necessary in future studies.

Our results are consistent with a recent review by Schneider *et al.*, which found that roughly half of potential SJS, TEN, and erythema multiforme cases identified using administrative data were validated after expert review.¹⁴ That review found relatively scarce recent literature on erythema multiforme and related conditions. In fact, only three studies (published between 1990 and 2001) provided validated algorithms for case finding, and all were based on ICD-9 code 695.1.^{15–18} In these studies, the PPV of ICD-9 code 695.1 ranged from 53.7% to 59.6%. These studies, however, did not assess the accuracy of recent diagnostic coding changes that became effective in October 2008, nor did they assess whether clinical or demographic characteristics could be used to improve case-finding efficiency.

There were some limitations to our study. To estimate the number of potential SJS/TEN cases in the larger population, we applied the results of our logistic regression model to the original study population. It is likely that there is some degree of model overfitting, resulting in an overestimation of the number of potential cases. Our more conservative sensitivity analysis used the lower confidence limits of the model estimates and still found a relatively large number of possible cases (475 versus 857). Our results were based on a relative number of abstracted cases (276), which inherently limited our model building efforts and also our ability to look at specific AEDs. Finally, the medical records were not always able to conclusively differentiate SJS and TEN from erythema multiforme major. As future studies may want to study these conditions separately, we may have overestimated the number of available SJS/TEN patients.

There is interest in understanding the risk for developing SJS and TEN after exposure to specific medications and among carriers of different genetic variants. While we found a large number of potential cases, a prospective enrollment study would face the challenges of losing patients because of death, disenrollment, or personal reasons. There may still be limited ability to conduct genetic studies aimed at identifying genes that confer differential susceptibility by specific AEDs, and broader national or international efforts may be required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- The combination of recently introduced ICD-9 codes, along with extended LOS, identified a large group of patients with a high likelihood of having SJS/TEN.
- This study suggests that case finding could be carried out efficiently using a small combination of codes, but it is likely that further validation of case status chart review will continue to be necessary in future studies.
- There may still be limited ability to conduct genetic studies aimed at identifying genes that confer differential susceptibility for SJS/TEN by specific antiepileptic medications and broader (national or international) efforts may be required.

Table 1.

Clinical characteristics of patients before diagnosis and during hospitalization

Variables	Level	Early group pre-October 2008 codes (n = 3143)			Late group post-October 2008 codes (n = 1836)			Non-specific code Group 3 (n = 51 972)		
		n (%)			n (%)			n (%)		
Medication exposure in 60 days prior to index date										
Antibiotics	No	1796 (57.1)			1029 (56.0)			30752 (59.2)		
	Yes	1347 (42.9)			807 (44.0)			21220 (40.8)		
Anticonvulsants	No	2719 (86.5)			1545 (84.2)			41081 (79.0)		
	Yes	424 (13.5)			291 (15.8)			10891 (21.0)		
Gout medications	No	3022 (96.2)			1736 (96.0)			48584 (93.5)		
	Yes	121 (3.8)			73 (4.0)			3388 (6.5)		
Infections in 30 days prior to or following index date (except as noted)										
Any viral infection	No	2929 (93.2)			1735 (94.5)			48947 (94.2)		
	Yes	214 (6.8)			101 (5.5)			3025 (5.8)		
Herpes	No	3098 (98.6)			1806 (98.4)			51264 (98.6)		
	Yes	45 (1.4)			30 (1.6)			708 (1.4)		
Influenza	No	3114 (99.1)			1820 (99.1)			51591 (99.3)		
	Yes	29 (0.9)			16 (0.9)			381 (0.7)		
Hepatitis (in 14 days prior to or following index date)	No	3035 (96.6)			1788 (97.4)			50308 (96.8)		
	Yes	108 (3.4)			48 (2.6)			1664 (3.2)		
Epstein-Barr	No	3117 (99.2)			1827 (99.5)			51805 (99.7)		
	Yes	26 (0.8)			9 (0.5)			167 (0.3)		
Enterovirus	No	3129 (99.6)			1834 (99.9)			51755 (99.6)		
	Yes	14 (0.4)			2 (0.1)			217 (0.4)		
Any bacterial	No	3021 (96.1)			1785 (97.2)			50240 (96.7)		
	Yes	122 (3.9)			51 (2.8)			1732 (3.3)		
Streptococcal	No	3051 (97.1)			1805 (98.3)			50355 (96.9)		
	Yes	92 (2.9)			31 (1.7)			1617 (3.1)		
Mycobacteria	No	3138 (99.8)			1831 (99.7)			51889 (99.8)		

Variables	Level	Early group pre-October 2008 codes (n = 3143)		Late group post-October 2008 codes (n = 1836)		Non-specific code Group 3 (n = 51 972)	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mycoplasma	Yes	5 (0.2)		5 (0.3)		83 (0.2)	
	No	3119 (99.2)		1820 (99.1)		51957 (100.0)	
Any fungal	Yes	24 (0.8)		16 (0.9)		15 (0.0)	
	No	3047 (96.9)		1789 (97.4)		49727 (95.7)	
Coccidiomycosis	Yes	96 (3.1)		47 (2.6)		2245 (4.3)	
	No	3134 (99.7)		1834 (99.9)		51906 (99.9)	
Dermatophytosis	Yes	9 (0.3)		2 (0.1)		66 (0.1)	
	No	3056 (97.2)		1791 (97.5)		49802 (95.8)	
	Yes	87 (2.8)		45 (2.5)		2170 (4.2)	
Clinical characteristics at index date or during hospitalization							
Nephritis	No	3138 (99.8)		1830 (99.7)		51773 (99.6)	
	Yes	5 (0.2)		6 (0.3)		199 (0.4)	
Pneumonitis	No	3137 (99.8)		1828 (99.6)		51787 (99.6)	
	Yes	6 (0.2)		8 (0.4)		185 (0.4)	
Myocarditis	No	3139 (99.9)		1836 (100.0)		51928 (99.9)	
	Yes	4 (0.1)		0 (0.0)		44 (0.1)	
Cellulitis	No	2711 (86.3)		1588 (86.5)		43251 (83.2)	
	Yes	432 (13.7)		248 (13.5)		8721 (16.8)	
Conjunctivitis	No	3135 (99.7)		1833 (99.8)		51956 (100.0)	
	Yes	8 (0.3)		3 (0.2)		16 (0.0)	
Mucositis	No	3018 (96.0)		1698 (92.5)		51 163 (98.4)	
	Yes	125 (4.0)		138 (7.5)		809 (1.6)	
Sepsis	No	3053 (97.1)		1760 (95.9)		49 972 (96.2)	
	Yes	90 (2.9)		76 (4.1)		2000 (3.8)	
Topical burn treatments	No	2789 (88.7)		1639 (89.3)		49 791 (95.8)	
	Yes	354 (11.3)		197 (10.7)		2181 (4.2)	
ICU stay	No	2735 (87.0)		1607 (87.5)		47 413 (91.2)	
	Yes	408 (13.0)		229 (12.5)		4559 (8.8)	
Steroid therapy	No	2214 (70.4)		1263 (68.8)		43 426 (83.6)	

Variables	Level	Early group pre-October 2008 codes (n = 3143)		Late group post-October 2008 codes (n = 1836)		Non-specific code Group 3 (n = 51 972)	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
IVIIG	Yes	929 (29.6)	573 (31.2)	8546 (16.4)			
	No	3096 (98.5)	1802 (98.1)	51785 (99.6)			
Radiation exposure in 60 days prior to index	Yes	47 (1.5)	34 (1.9)	187 (0.4)			
	No	3092 (98.4)	1822 (99.2)	51453 (99.0)			
SLE	Yes	51 (1.6)	14 (0.8)	519 (1.0)			
	No	3051 (97.1)	1777 (96.8)	50948 (98.0)			
History of other collagen-vascular dx	Yes	92 (2.9)	59 (3.2)	1024 (2.0)			
	No	2715 (86.4)	1570 (85.5)	45199 (87.0)			
Charlson comorbidity index	Yes	428 (13.6)	266 (14.5)	6773 (13.0)			
	0	2190 (69.7)	1336 (72.8)	30525 (58.7)			
	1	294 (9.4)	168 (9.2)	5454 (10.5)			
	2	218 (6.9)	128 (7.0)	5552 (10.7)			
	3+	441 (14.0)	204 (11.1)	10441 (20.1)			

Table 2.

Demographic characteristics of patients in the three study groups

		Early group pre-October 2008 codes (n = 3143)	Late group post-October 2008 codes (n = 1836)	Non-specific code Group 3 (n = 51 972)
		n (%)	n (%)	n (%)
Gender	Female	1755 (55.8)	1029 (56.0)	29 890 (57.5)
	Male	1376 (43.8)	799 (43.5)	21 877 (42.1)
	Not stated	12 (0.4)	8 (0.4)	205 (0.4)
Race	White	918 (29.2)	530 (28.9)	27 128 (52.2)
	Black	232 (7.4)	144 (7.8)	3013 (5.8)
	Asian	163 (5.2)	111 (6.0)	2985 (5.7)
	Other/not stated	1830 (58.2)	1051 (57.2)	18 846 (36.3)
Hispanic	No/unknown/not stated	2910 (92.6)	1716 (93.5)	47 399 (91.2)
	Yes	233 (7.4)	120 (6.5)	4573 (8.8)
Age	(Missing)	12 (0.4)	8 (0.4)	204 (0.4)
	45	1585 (50.4)	868 (47.3)	13 198 (25.4)
	>45–60	621 (19.8)	412 (22.4)	12 018 (23.1)
	>60–75	522 (16.6)	347 (18.9)	13 700 (26.4)
	75+	403 (12.8)	201 (10.9)	12 852 (24.7)
	2001	256 (8.1)	n/a	2656 (5.1)
Index year	2002	262 (8.3)	n/a	2879 (5.5)
	2003	283 (9.0)	n/a	3221 (6.2)
	2004	469 (14.9)	n/a	4652 (9.0)
	2005	502 (16.0)	n/a	4915 (9.5)
	2006	488 (15.5)	n/a	4972 (9.6)
	2007	461 (14.7)	n/a	5074 (9.8)
	2008	422 (13.4)	199 (10.8)	5422 (10.4)
	2009	n/a	567 (30.9)	5684 (10.9)
	2010	n/a	543 (29.6)	6050 (11.6)
	2011	n/a	450 (24.5)	5396 (10.4)
Discharge status	2012	n/a	77 (4.2)	1051 (2.0)
	Alive	2337 (74.4)	1172 (63.8)	42 851 (82.5)

	Early group pre-October 2008 codes (n = 3143)	Late group post-October 2008 codes (n = 1836)	Non-specific code Group 3 (n = 51 972)
	n (%)	n (%)	n (%)
Dead	153 (4.9)	57 (3.1)	3304 (6.4)
Not specified	653 (20.8)	607 (33.1)	5817 (11.2)
Hospitalized on index date?			
Not hospitalized	0 (0.0)	978 (53.3)	0 (0.0)
Hospitalized at index	3143 (100.0)	798 (43.5)	51 972 (100.0)
Hospitalized after index	0 (0.0)	60 (3.3)	0 (0.0)
Not hospitalized	0 (0.0)	996 (54.2)	0 (0.0)
Length of hospital stay			
2 or fewer days	710 (22.6)	123 (6.7)	13 213 (25.4)
3 to 5 days	1130 (36.0)	262 (14.3)	16 528 (31.8)
6 to 13 days	795 (25.3)	283 (15.4)	12 709 (24.5)
14 or more days	508 (16.2)	172 (9.4)	9522 (18.3)

Table 3.

Results of case adjudication

	No	Yes	Total
Group 1			
Not hospitalized	—	—	—
Hospitalized	69 (73%)	25 (27%)	
Total	69 (73%)	25 (27%)	94 (100%)
Group 2			
Not hospitalized	41 (85%)	7 (15%)	
Hospitalized	5 (50%)	5 (50%)	
Total	46 (79%)	12 (21%)	58 (100%)
Group 3			
Not hospitalized	—	—	
Hospitalized	122 (98%)	2 (2%)	
Total	122 (98%)	2 (2%)	124 (100%)
Total	237	39	276

Table 4.

Expected number of cases in each strata when regression results applied to the entire study population

Group	Length of hospital stay	Modeled probability [†]	95% lower CI	95% upper CI	Number in population	Estimated no. of cases using modeled probability	Estimated no. of cases using 95% lower confidence limit
1	Not hospitalized	—	—	—	—	—	—
1	2 or fewer days	0.078	0.025	0.221	710	56	18
1	3 to 5 days	0.286	0.166	0.448	1130	324	187
1	6 to 13 days	0.283	0.133	0.504	795	225	106
1	14 or more days	0.766 [*]	0.467	0.925	508	389	237
2	Not hospitalized	0.146	0.071	0.276	996	145	71
2	2 or fewer days	0.220	0.049	0.609	123	27	6
2	3 to 5 days	0.572 [*]	0.253	0.840	262	150	66
2	6 to 13 days	0.567 [*]	0.228	0.853	283	160	65
2	14 or more days	0.916 [*]	0.621	0.986	172	158	107
3	Not hospitalized	—	—	—	—	—	—
3	2 or fewer days	0.002	0.000	0.013	13 213	23	3
3	3 to 5 days	0.008	0.001	0.045	16 528	136	24
3	6 to 13 days	0.008	0.001	0.049	12 709	103	16
3	14 or more days	0.064	0.015	0.233	9522	606	143
Total					56 951	2502	1049

^{*} Indicates the four groups with modeled probabilities greater than 50%. The total number of patients identified in these four groups totals 1225, of which 475–857 are estimated to be valid cases.[†] Modeled probabilities obtained from model using 276 adjudicated cases (see text for further details).