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Epidemiology and Outcomes of Hospitalizations With Invasive Aspergillosis in the United States, 2009–2013

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Background. Though invasive aspergillosis (IA) complicates care of up to 13% of patients with immunocompromise, little is known about its morbidity and mortality burden in the United States.

Methods. We analyzed the Health Care Utilization Project's data from the Agency for Healthcare Research and Quality for 2009–2013. Among subjects with high-risk conditions for IA, IA was identified via *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 117.3, 117.9, and 484.6. We compared characteristics and outcomes between those with (IA) and without IA (non-IA). Using propensity score matching, we calculated the IA-associated excess mortality and 30-day readmission rates, length of stay, and costs.

Results. Of the 66 634 683 discharged patients meeting study inclusion criteria, 154 888 (0.2%) had a diagnosis of IA. The most common high-risk conditions were major surgery (50.1%) in the non-IA and critical illness (41.0%) in the IA group. After propensity score matching, both mortality (odds ratio, 1.43; 95% confidence interval, 1.36–1.51) and 30-day readmission (1.39; 1.34–1.45) rates were higher in the IA group. IA was associated with 6.0 (95% confidence interval, 5.7–6.4) excess days in the hospital and $15 542 ($13 869–$17 215) in excess costs per hospitalization.

Conclusions. Although rare even among high-risk groups, IA is associated with increased hospital mortality and 30-day readmission rates, excess duration of hospitalization, and costs. Given nearly 40 000 annual admissions for IA in the United States, the aggregate IA-attributable excess costs may reach $600 million annually.

Keywords. invasive aspergillosis; epidemiology; outcomes; hospital.

Although invasive aspergillosis (IA) occurs infrequently among immunocompetent individuals, it remains a major issue in the care of patients who have undergone either stem cell or solid organ transplantation, with the prevalence over 10% in select populations [1–7]. There are few broadly generalizable data available on the current morbidity and mortality burden from IA hospitalizations in the United States. One analysis based on a national sample of all US hospitalizations from >2 decades ago indicated that IA-associated mortality neared 20% [8]. However, few large analyses, if any, have examined this issue in more recent years. Furthermore, and underscoring the burden of IA, that analysis estimated that the national costs related to IA hospitalizations topped $600 million.

Such older estimates regarding outcomes related to IA require reassessment. Much has changed in the last 20 years, in terms of IA prevalence and severity, its underlying associated conditions, and its treatment. Several reports suggest that IA has increased in prevalence, a phenomenon most likely due to several factors, including improved diagnostics, an overall escalation in the use of immunosuppressive therapies, and an increased number of organ transplantations performed in recent decades [9–11]. Given the expanded spectrum of disease severity among patients now eligible for aggressive immunosuppressive treatments, and newer treatment options for IA, it is unclear what these countervailing factors imply for outcomes associated with IA. Therefore, to derive more recent estimates of the prevalence and costs related to acute hospitalizations associated with IA, we examined a nationally representative sample of patients admitted to acute-care hospitals in the United States with a diagnosis of IA.

METHODS

Study Design

We performed a retrospective cohort study to explore the epidemiology and outcomes of hospitalizations with IA in the United States. The outcomes of interest were hospital mortality rate, length of stay (LOS), costs, and 30-day readmission rate.

Data Sources

We analyzed the National (formerly "Nationwide") Inpatient Sample (NIS), part of the Health Care Utilization Project administered by the Agency for Healthcare Research and Quality for the years 2010–2013. The NIS is a large, all-payer

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database of inpatient hospitalizations, which can be used to derive nationally representative estimates of hospital inpatient stays. (For more information on the NIS database, see https://www.hcup-us.ahrq.gov/nisoverview.jsp.) The NIS consists of a stratified sample of hospital discharge records from approximately 1000 participating facilities, representing about 20% of all acute-care hospitals in the United States.

The unit of reporting in the NIS database is a hospital discharge. The database includes data on patient demographics, diagnoses, and procedures and in-hospital mortality rates, as well as hospital charges and LOS for each discharge. Additional data files, linkable to discharges in the NIS database, provide data on hospital characteristics, illness severity measures, and cost-to-charge conversion coefficients for each individual institution in the database. Complex survey methods exist to develop national and regional estimates for conditions addressed in the database. The Agency for Healthcare Research and Quality undertakes an assessment of completeness and data quality, and documentation is provided with the data set. Data quality checks are limited to logical issues (eg, birth date precedes age at hospital admission; excessively low total charges or long LOS; age <10 or >55 years on a maternal record; mixed neonatal and maternal records). No chart reviews are undertaken by the Agency.

Because the NIS does not report 30-day readmission rates, we relied on data in the State Inpatient Databases (SID), also part of the Health Care Utilization Project, from 4 geographically diverse US states (California [available only for 2009–2011], Florida, Iowa, and New York) for 2009–2013. Although these databases are similar to the NIS, they are confined to the individual states. However, it is possible to identify readmissions owing to the way individual patients are tracked within the state, provided that they occurred within the same state and year as the index hospitalization.

Case Identification

IA hospitalizations were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 117.3, 117.9, and 484.6, shown to be sensitive in detecting IA [12]. We used *ICD-9-CM* codes, procedure codes, and diagnosis-related groups to identify discharged patients at high risk for IA [13, 14] (see Supplementary Material). These categories were as follows: stem cell transplant, solid organ transplant, critical illness (including mechanical ventilation, trauma, sepsis), major surgery, mild-to-moderate immunocompromise (includes renal disease, lupus and a variety of blood disorders), severe immunocompromise (including leukemia, lymphoma, and chemotherapy), and other (including pneumonia, chronic obstructive pulmonary disease, and human immunodeficiency virus infection). Discharges falling outside these definitions were excluded from analyses.

Outcome Variables and Follow-up

Hospital mortality rate served as the primary end point of the study. As secondary outcomes, we analyzed hospital LOS in days and hospital costs in US dollars. In the SID analysis only, we examined 30-day readmission rates among survivors of the index hospitalization. The groups were followed up until discharge from or death in the hospital. For the 30-day readmission, survivors of the index hospitalization were followed up for another 30 days.

Statistical Analyses

We conducted the following analyses in the NIS, and repeated them in the SID data with the addition of the 30-day readmission outcome. We compared hospital mortality rates, LOS, costs and 30-day readmission rates among all high-risk discharged patients with concomitant diagnosis of IA and those without IA (non-IA). We examined demographic, clinical, hospital, and discharge characteristics in these groups. Means (with standard deviation) and medians (with interquartile range) were calculated for continuous variables, and counts and proportions for categorical variables. All statistics took the weighted nature of the data into account. Continuous variables were compared between the 2 groups using Student t or the Wald tests, and categorical variables using χ^2 tests. All inferences were 2 tailed. Statistical significance was defined as P values <.05.

To adjust for confounding in all outcomes, we developed a single propensity score using a probit regression model with IA status as the outcome based on patient demographics (age, race, sex), patient type (urgent, emergent elective, trauma), admission source, weekend admission status, comorbid conditions (based on the Elixhauser classification [15]), number of discharge diagnoses and procedures, the defined high-risk groups, and hospital characteristics (hospital size, location, teaching status, and urbanicity). Propensity score matching was conducted using a greedy 5:3 digit algorithm [16, 17]. The covariates in the propensity regression model were compared after matching to see if they were significantly different, and standardized differences between covariates by IA status were also derived. Covariate balance was a priori determined to exist if all covariates were nonsignificantly different after matching ($P < .05$) or, if they were significantly different, the standardized difference was <0.1.

For mortality and 30-day readmission outcomes, we constructed a weighted conditional logistic regression model on the matched pairs, with the predictor being IA status. As a sensitivity analysis, we repeated the analysis using logistic regression for all patients who met our study criteria, incorporating all the predictors used to estimate the propensity of IA along with a new variable denoting IA status. In this sensitivity analysis, we examined both spline terms for age and clinically plausible interactions during the construction of the logistic regression model. The model fit was assessed with the Hosmer-Lemeshow goodness-of-fit for model calibration and the area under the receiver operating curve for model discrimination.

For the continuous outcomes of LOS and hospital costs, the method was repeated after taking into account the continuous nature of the outcomes. Namely, a weighted linear regression

model on the matched pairs was constructed as the principal analysis. As a sensitivity analysis, generalized linear models were used on all patients who met our study criteria with the covariates in the propensity score along with a variable for IA status. Because the continuous outcome data were skewed, a logarithmic link was used, along with a gamma distribution to improve model fit. Statistical analyses were performed using Stata/MP software (version 13.1 for Windows; StataCorp).

We report in detail the NIS findings since the SID analyses were done largely to explore the 30-day readmission outcome (unavailable in the NIS) and to confirm the findings observed in the NIS data set. Consequently, the details of the SID-based cohort can be found in the Supplementary Material.

RESULTS

Among a total of 148 533 858 patients discharged from years 2010 through 2013 in the NIS database, 66 634 683 met the study inclusion criteria, of whom 154 888 (0.2%) had a diagnosis of IA (Figure 1). The baseline characteristics of the 2 groups are shown in Table 1. The discharges were spread evenly across the 4 years of the study period in both IA and non-IA groups. Although the mean ages (and standard deviations) in the 2 groups were similar, the small difference was statistically significant ($P < .001$), owing in part to the large sample size. Patients with IA were more likely to be male (50.9% in the IA vs 46.7% in non-IA group; $P < .001$) and African-American (15.3% vs 12.5%; $P < .001$) (Table 1).

As expected, there were significant differences between groups in terms of high-risk condition distributions (Figure 2). For example, the most common reason for identification as high risk in the non-IA group was major surgery (50.1%), whereas in the IA group it was critical illness (41.0%). Stem cell transplant (0.3%) and mild-to-moderate immunocompromise (2.5%) were the least likely criteria for being high risk in non-IA and IA groups, respectively. The burden of both chronic conditions (median number of Elixhauser comorbid conditions [interquartile range], 3 [1–5] in non-IA vs 4 [3–6] in IA group; $P < .001$) and the number of procedures done during hospitalization (median, 2 [1–3] vs 3 [1–6], respectively ; $P < .001$) was higher in the IA than in the non-IA group. Geographically, the plurality of all discharges occurred in the Western region in both groups. Despite the statistically significant differences, there were no clinically notable differences between regional contributions to the IA and non-IA groups (Table 1). Although urban teaching hospitals provided the bulk of discharges in both groups, the proportion coming from this type of institution in the IA group was higher than in the non-IA group (59.4% vs 48.4%, respectively; $P < .001$, Table 1). Larger hospitals were more likely than smaller ones to contribute IA cases (Table 1).

The unadjusted outcomes for non-IA and IA groups are shown in Table 2. The hospital mortality rate among patients with IA (14.1%) was 4-fold higher than in the non-IA group (3.4%; $P < .001$). Similarly, there were large differences between groups in the LOS, hospital charges, and costs, with each being 2.5–4 times higher in the IA than in the non-IA group (Table 2).

Except for a handful of characteristics, propensity matching of 154 081 IA discharges (99.5%) eliminated intergroup differences (Table 3). Even where the differences remained statistically significant, no standardized difference was >0.034.

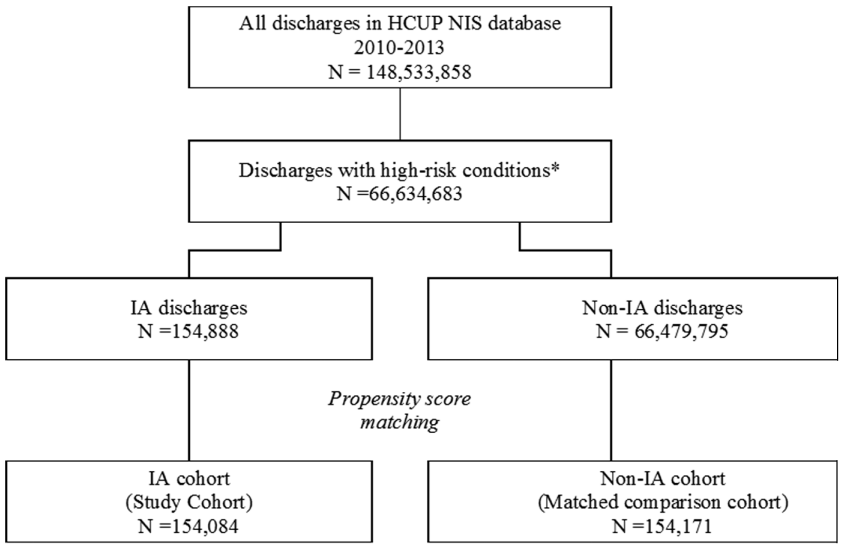

Figure 1. Study enrollment flow chart. High-risk conditions include stem cell and solid organ transplants, severe immunocompromise (leukemia/lymphoma, chemotherapy, other immune disorders, and long-term steroid use), critical illness (trauma, septicemia, necrotizing fasciitis, intracranial hemorrhage, and mechanical ventilation for ≥96 hours), mild-to- moderate immunocompromise (end-stage renal disease or hemodialysis, lupus, malignant solid tumors, diabetic ketoacidosis, and blood disorders), major surgery, and other conditions (pneumonia, chronic obstructive pulmonary disease, and human immunodeficiency virus infection). Abbreviations: HCUP, Health Care Utilization Project; IA, invasive aspergillosis; NIS, National Inpatient Sample.

Table 1. Baseline Characteristics, National Inpatient Sample Analysis[a]

Characteristic	Patients, No. (%)		*P* Value
	Non-IA Group (n = 66 479 795)	IA Group (n = 154 888)	
Demographic characteristics			
Sex			
Male	31 042 952 (46.7)	78 770 (50.9)	<.001
Female	35 405 502 (53.3)	76 118 (49.1)	
Age, y			
Mean (SD)	62.6 (17.9)	61.8 (16.8)	<.001
Median (IQR)	64 (51–77)	64 (52–74)	
Race			
White	44 526 259 (67.0)	100 68 (65.0)	<.001
Black	8 320 004 (12.5)	23 631 (15.3)	
Hispanic	5 248 792 (7.9)	12 228 (7.9)	
Asian or Pacific Islander	1 170 046 (1.8	3889 (2.5)	
Native American	383 561 (0.6)	676 (0.4)	
Other	1 561 063 (2.3)	4030 (2.6)	
Data missing	5 270 070 (7.9)	9752 (6.3)	
Primary expected payer			
Medicare	36 495 542 (54.9)	87 822 (56.7)	<.001
Medicaid	6 949 615 (10.5)	20 611 (13.3)	
Private	17 239 637 (25.9)	36 877 (23.8)	
Self-pay	3 056 800 (4.6)	4653 (3.0)	
No charge	329 595 (0.5)	612 (0.4)	
Other	2 253 531 (3.4)	4104 (2.6)	
Data missing	155 074 (0.2)	209 (0.1)	
Year of admission			
2010	17 287 324 (26.0)	39 284 (25.4)	.56
2011	17 695 983 (26.6)	40 364 (26.1)	
2012	15 807 892 (23.8)	38 390 (24.8)	
2013	15 688 596 (23.6)	36 850 (23.8)	
Admission characteristics			
Admission type			
Emergency	17 288 605 (26.0)	41 892 (27.0)	<.001
Urgent	5 116 128 (7.7)	15 200 (9.8)	
Elective	8 731 135 (13.1)	12 089 (7.8)	
Delivery	332 851 (0.5)	221 (0.1)	
Trauma center	3073 (0.0)	<10[b] (0.0)	
Other/data missing	35 008 003 (52.7)	85 481 (55.2)	
Emergency department service	38 184 223 (57.4)	92 437 (59.7)	<.001
Weekend admission	12 463 539 (18.7)	31 548 (20.4)	<.001
Hospital characteristics			
Census region			
Northeast	12 497 745 (18.8)	28 761 (18.6)	.007
Midwest	15 659 097 (23.6)	32 394 (20.9)	
West	25 910 920 (39.0)	62 268 (40.2)	
South	12 412 034 (18.7)	31 466 (20.3)	
Location/teaching status			
Rural	7 705 468 (11.6)	10 152 (6.6)	<.001
Urban nonteaching	26 165 688 (39.4)	52 016 (33.6)	
Urban teaching	32 185 686 (48.4)	91 927 (59.4)	
Data missing	422 953 (0.6)	794 (0.5)	
Size			
Small (1–49 beds)	8 538 228 (12.8)	15 168 (9.8)	<.001
Medium (50–99 beds)	16 162 746 (24.3)	32 689 (21.1)	
Large (≥100 beds)	41 355 868 (62.2)	106 238 (68.6)	
Data missing	422 953 (0.6)	794 (0.5)	
Hospital IA caseload, %			
Mean (SD)	0.2 (0.2)	0.5 (0.8)	…
Median (IQR)	0.2 (0.1–0.3)	0.3 (0.2–0.6)	<.001
Clinical characteristics			
High-risk conditions			
Stem cell transplant	193 249 (0.3)	5305 (3.4)	<.001
Solid organ transplant	875 378 (1.3)	7708 (5.0)	
Critical illness	14 175 190 (21.3)	63 465 (41.0)	
Major surgery	33 281 840 (50.1)	54 799 (35.4)	
Severe immunocompromise	6 619 094 (10.0)	12 711 (8.2)	
Mild-to-moderate immunocompromise	3 508 553 (5.3)	3883 (2.5)	
Other[c]	7 826 491 (11.8)	10 018 (6.5)	
Elixhauser comorbid conditions[d]			
AIDS/HIV	294 562 (0.4)	1153 (0.7)	<.001
Alcohol abuse	3 039 272 (4.6)	6132 (4.0)	<.001
Blood loss anemia	1 136 933 (1.7)	2307 (1.5)	<.001
Chronic pulmonary disease	18 218 914 (27.4)	50 872 (32.8)	<.001
Coagulopathy	4 103 153 (6.2)	26 129 (16.9)	<.001
Congestive heart failure	7 650 797 (11.5)	27 690 (17.9)	<.001
Deficiency anemia	13 992 274 (21.0)	50 308 (32.5)	<.001
Depression	7 998 384 (12.0)	19 398 (12.5)	<.001
Diabetes, complicated	3 694 396 (5.6)	11 452 (7.4)	<.001
Diabetes, uncomplicated	14 062 429 (21.2)	34 321 (22.2)	<.001
Drug abuse	2 132 535 (3.2)	5941 (3.8)	<.001
Fluid and electrolyte disorders	18 524 222 (27.9)	81 222 (52.4)	<.001
Hypertension	37 299 088 (56.1)	76 275 (49.2)	<.001
Hypothyroidism	8 314 191 (12.5)	17 152 (11.1)	<.001
Liver disease	2 379 727 (3.6)	8723 (5.6)	<.001
Lymphoma	662 042 (1.0)	4752 (3.1)	<.001
Metastatic cancer	2 206 932 (3.3)	7438 (4.8)	<.001
Neurodegenerative disorders	5 470 468 (8.2)	15 927 (10.3)	<.001
Obesity	8 096 351 (12.2)	15 438 (10.0)	<.001
Paralysis	1 845 579 (2.8)	8371 (5.4)	<.001
Peptic ulcer disease, no bleeding	29 401 (0.0)	116 (0.1)	.007
Peripheral vascular disorders	5 022 891 (7.6)	12 471 (8.1)	.007
Psychosis	3 025 718 (4.6)	7640 (4.9)	.003
Pulmonary circulation disorders	1 948 873 (2.9)	10 934 (7.1)	<.001
Renal failure	10 182 469 (15.3)	33 219 (21.4)	<.001
Rheumatoid arthritis/collagen vascular diseases	2 303 887 (3.5)	6761 (4.4)	<.001
Solid tumor without metastasis	1 987 297 (3.0)	6081 (3.9)	<.001
Valvular disease	2 938 867 (4.4)	8180 (5.3)	<.001
Weight loss	4 377 595 (6.6)	40 076 (25.9)	<.001
Elixhauser comorbid conditions, total No.			
Mean (SD)	3.1 (2.2)	4.3 (2.3)	…
Median (IQR	3 (1–5)	4 (3–6)	<.001

Table 1. Continued

Characteristic	Patients, No. (%)		
	Non-IA Group (n = 66 479 795)	IA Group (n = 154 888)	*P* Value
Discharge diagnoses, No.			
Mean (SD)	11.3 (6.0)	17.5 (6.3)	…
Median (IQR)	10 (7–15)	17 (13–23)	<.001
Procedures, No.			
Mean (SD)	2.2 (2.4)	4.5 (4.5)	…
Median (IQR)	2 (1–3)	3 (1–6)	<.001
Abdominal procedures/ operations	5 738 103 (8.6)	6373 (4.1)	<.001

Since the distributions were non-normal, the appropriate comparison values are provided for the median but not the mean values.

Abbreviations: HIV, human immunodeficiency virus; IA, invasive aspergillosis; IQR, interquartile range; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]The Agency for Healthcare Research and Quality prohibits reporting on <10 cases.

[c]Includes pneumonia, chronic obstructive pulmonary disease, and HIV infection.

[d]Total adds up to >100% because it is possible to have >1 comorbid condition per discharge.

Table 4 lists hospital outcomes after propensity matching. Adjusted mortality rates remained significantly higher with IA than without (14.1% vs 10.3%; $P < .001$; odds ratio, 1.43; 95% confidence interval [CI], 1.36–1.51). Similarly, relative to no IA, IA was associated with an excess attributable LOS of 6.0 days (95% CI, 5.7–6.4 days) and an excess cost of $15 542 ($13 869–$17 215).

The results from the SID analyses revealed similar findings and outcomes by IA status compared with those seen in the NIS (Supplementary Material). The propensity-adjusted 30-day readmission rate was higher in the IA than in the non-IA group (18.0% vs 13.7%; $P < .001$). In a logistic regression, IA was associated with significantly higher odds of readmission within 30 days (odds ratio, 1.39; 95% CI, 1.34–1.45), relative to no IA.

DISCUSSION

We demonstrate that IA remains a rare event among patients hospitalized in the United States, even in the presence of a high-risk condition. At the same time, IA adds substantially not only to the risk of death, but also to the expenses of hospitalization. Namely, IA contributes 6 additional days, and >$15 000 in additional costs, per case. Furthermore, a diagnosis of IA is associated with a significant increase (approximately 40%) in the odds of a 30-day rehospitalization among survivors.

Few current data are available on the clinical and economic outcomes of hospitalizations involving IA. A study using 1996 NIS data provides the most generalizable results on the outcomes we evaluated [8]. Compared with the findings from that earlier study, we document a marked rise in the prevalence of IA among patients undergoing acute hospitalizations. Although 1996 saw approximately 10 000 IA hospitalizations, our data suggest a quadrupling of this volume, with the attendant increase in the incidence from 3/10 000 to 10/10 000 discharges overall. At the same time, crude mortality has dropped from 19% to 14%, and excess LOS and costs have also fallen from 12 to 6 days and from $51 000 to $15 000 per admission, respectively [8].

It is precisely this drop in hospital utilization that seems responsible for the overall stability of total national costs for IA hospitalizations at $600 million in the face of a dramatic rise in prevalence. That is, although the incidence of IA has increased, outcomes for these patients seem to have improved substantially. Consequently, the net total economic burden has

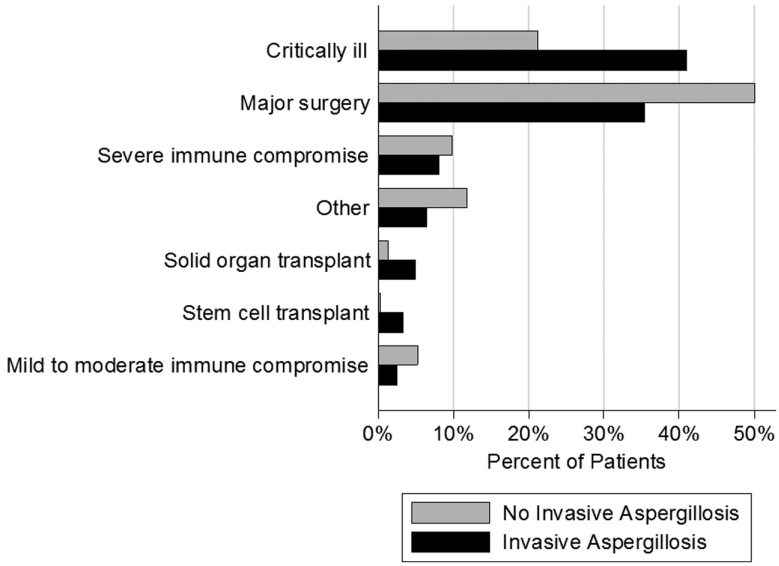

Figure 2. High-risk conditions in the comparator groups in the National Inpatient Sample. The invasive aspergillosis (IA) and non-IA groups differed significantly ($P < .001$). The "Other" designation includes pneumonia, chronic obstructive pulmonary disease, and human immunodeficiency virus infection.

Table 2. Unadjusted Hospital Outcomes

Outcome	Non-IA Group (n = 66 479 795)	IA Group (n = 154 888)	*P* Value
Mortality rate, No. (%)	2 254 516 (3.4)	21 870 (14.1)	<.001
Length of stay, d			
Mean (SD)	5.6 (6.9)	17.9 (20.2)	…
Median (IQR)	4 (2–7)	12 (6–24)	<.001
Total charges, $			
Mean (SD)	53 133 (78 632)	185 626 (287 748)	…
Median (IQR)	32 401 (17 483–60 128)	91 978 (40 329–215 168)	<.001
Total costs, $			
Mean (SD)	14 860 (20 102)	50 661 (74 719)	…
Median (IQR)	9772 (5695–16 838)	25 823 (12 171–59 895)	<.001

Since the distributions were non-normal, the appropriate comparison values are provided for the median but not the mean values.
Abbreviations: IA, invasive aspergillosis; IQR, interquartile range; SD, standard deviation.

probably fallen when one incorporates the impact of healthcare inflation, because our findings are reported in nominal dollars. As mentioned above, it is important to reiterate that the increase in the volume of IA may be due to improved diagnostics, an overall escalation in the use of immunosuppressive therapies, and an increased number of organ transplantations performed in recent decades [9–11].

Our finding of an approximate 40% increase in the odds of 30-day readmission associated with IA represents a novel and important observation, particularly in the context of current cost-containment efforts and dwindling hospital reimbursements. The passage of the Affordable Care Act created the Hospital Readmission Reduction Program, under which the Centers for Medicare and Medicaid Services (CMS) is mandated to help reduce hospital readmissions for select conditions [18]. Although the initial focus of the program was on acute myocardial infarction, congestive heart failure, and pneumonia, the list of conditions has been expanding over time and is expected to continue to do so [18, 19]. Under this regulation, hospitals incur reimbursement cuts if their readmission rates exceed those expected. Although IA is not included on the most recent list of conditions under CMS scrutiny, it is very likely that patients with IA require readmissions for many of the conditions already tracked by the CMS. Thus, hospitals may suffer financial punishment simply for caring for an increasingly complex cohort of patients. This further reinforces the imperative to focus on preventive efforts for IA.

Our study has a number of strengths. Because we relied on a large nationally representative sample of high-risk discharges, our results are broadly generalizable to all US hospitals. Although the data supporting the examination of 30-day readmission rates among patients discharged alive after an IA hospitalization are limited to 4 states, the states were chosen based on their geographic diversity, which increases the generalizability of the findings [20]. In addition, the sample size and number of covariates in the data set allowed us to adjust for confounding in a statistically rigorous manner. It is also important to stress that no other systematic information exists regarding the risk for readmission in persons with IA.

At the same time, our analysis suffers from a number of potential limitations. First, we relied on administrative codes, and not on clinical data, to identify both the high-risk groups and IA. This may predispose our case definitions to errors of misclassification, though methods similar to ours have been used successfully in both high-risk patients and IA [8, 12, 14]. Findings from another study, however, indicate that the IA *ICD-9-CM* codes are prone to overestimate the prevalence of IA [12]. This type of misclassification would be expected to reduce the observed differences between IA and non-IA groups. Consequently, IA may indeed have an even greater impact on the outcomes than we were able to detect. This idea is supported by the fact that studies relying on clinical definition for IA consistently report higher associated mortality rates [21].

Second, because of the cross-sectional nature of the data set, it was not possible to ascertain the temporal connection between the high-risk condition of interest and IA. Third, because we were unable to pinpoint the time of onset of IA, the disparities in the adjusted hospital LOS and costs cannot be directly associated with IA itself; that is, it is possible that at least some of the increase in the LOS (and related costs) in the IA group was a risk factor for, rather than a consequence of, IA. At the same time, at least some of the adjusted LOS and cost differences are likely to be directly attributable to IA, because nosocomial complications in general are known to affect LOS and costs. Moreover, it is reassuring that propensity matching greatly reduced confounding from the variables in the database between comparator groups.

Fourth, no treatment information is available in the current data set, so we were unable to explore its potential impact on the outcomes. Specifically, we cannot stratify by the timing of treatment onset or by the specific options used. Fifth, though we note a dramatic reduction in the IA-associated LOS compared with prior studies, our analysis reflects only acute-care hospitalization, excluding any downstream expenses associated either

Table 3. Characteristics of Groups After Propensity Matching

Characteristic	Patients, No. (%)[a] Non-IA Group (n = 154 186)	IA Group (n = 154 081)	*P* Value
Demographic characteristics			
Year of admission			
2010	39 142 (25.4)	38 916 (25.3)	
2011	40 225 (26.1)	39 930 (25.9)	.98
2012	38 025 (24.7)	38 385 (24.9)	
2013	36 795 (23.9)	36 850 (23.9)	
Sex			
Male	77 720 (50.4)	78 357 (50.9)	.30
Female	76 466 (49.6)	75 724 (49.1)	
Age, y			
Mean (SD)	62.9 (17.6)	61.9 (16.7)	<.001
Median (IQR)	64 (52–77)	64 (52–75)	.22
Race			
White	99 406 (64.5)	100 138 (65.0)	
Black	23 817 (15.4)	23 552 (15.3)	
Hispanic	12 014 (7.8)	12 135 (7.9)	
Asian or Pacific Islander	3900 (2.5)	3884 (2.5)	.84
Native American	647 (0.4)	619 (0.4)	
Other	4256 (2.8)	4011 (2.6)	
Data missing	10 147 (6.6)	9742 (6.3)	
Primary expected payer			
Medicare	88 315 (57.3)	87 387 (56.7)	
Medicaid	20 340 (13.2)	20 522 (13.3)	
Private	36 203 (23.5)	36 692 (23.8)	
Self-pay	4364 (2.8)	4597 (3.0)	.80
No charge	535 (0.3)	590 (0.4)	
Other	4236 (2.7)	4084 (2.7)	
Data missing	193 (0.1)	209 (0.1)	
Admission characteristics			
Admission type			
Emergency	41 796 (27.1)	41 451 (26.9)	
Urgent	12 866 (8.3)	14 962 (9.7)	
Elective	14 850 (9.6)	11 985 (7.8)	<.001
Delivery	964 (0.6)	221 (0.1)	
Trauma center	<10[b] (0.0)	<10[b] (0.0)	
Other/data missing	83 701 (54.3)	85 457 (55.5)	
Emergency department service	94 055 (61.0)	93 046 (60.4)	.33
Weekend admission	32 113 (20.8)	31 382 (20.4)	.17
Clinical characteristics			
High-risk conditions			
Stem cell transplant	4636 (3.0)	5271 (3.4)	
Solid organ transplant	7576 (4.9)	7698 (5.0)	
Critical illness	63 659 (41.3)	63 091 (40.9)	
Major surgery	51 254 (33.2)	51 560 (33.5)	.26
Severe immunocompromise	13 257 (8.6)	12 670 (8.2)	
Mild-to-moderate immunocompromise	3889 (2.5)	3848 (2.5)	
Other[c]	9915 (6.4)	9942 (6.5)	
Elixhauser comorbid conditions[d]			
AIDS/HIV	1329 (0.9)	1149 (0.7)	.18
Alcohol abuse	6089 (3.9)	6098 (4.0)	.96
Blood loss anemia	2460 (1.6)	2294 (1.5)	.32
Chronic pulmonary disease	52 134 (33.8)	50 602 (32.8)	.03
Coagulopathy	26 132 (16.9)	26 009 (16.9)	.84
Congestive heart failure	27 881 (18.1)	27 577 (17.9)	.58
Deficiency anemia	52 785 (34.2)	50 137 (32.5)	<.001
Depression	19 702 (12.8)	19 315 (12.5)	.39
Diabetes, complicated	34 308 (22.3)	34 195 (22.2)	.87
Diabetes, uncomplicated	11 614 (7.5)	11 401 (7.4)	.58
Drug abuse	6029 (3.9)	5896 (3.8)	.61
Fluid and electrolyte disorders	81 453 (52.8)	80 763 (52.4)	.41
Hypertension	75 429 (48.9)	75 987 (49.3)	.41
Hypothyroidism	17 144 (11.1)	17 080 (11.1)	.90
Liver disease	8788 (5.7)	8651 (5.6)	.67
Lymphoma	4721 (3.1)	4730 (3.1)	.96
Metastatic cancer	7464 (4.8)	7394 (4.8)	.81
Neurodegenerative disorders	16 022 (10.4)	15 868 (10.3)	.72
Obesity	15 415 (10.0)	15 365 (10.0)	.92
Paralysis	8573 (5.6)	8347 (5.4)	.47
Peptic ulcer disease, no bleeding	121 (0.1)	116 (0.1)	.88
Peripheral vascular disorders	12 270 (8.0)	12 416 (8.1)	.67
Psychosis	7446 (4.8)	7593 (4.9)	.58
Pulmonary circulation disorders	11 210 (7.3)	10 891 (7.1)	.34
Renal failure	34 368 (22.3)	33 067 (21.5)	.02
Rheumatoid arthritis/collagen vascular diseases	6463 (4.2)	6703 (4.4)	.36
Solid tumor without metastasis	6150 (4.0)	6057 (3.9)	.72
Valvular disease	8289 (5.4)	8123 (5.3)	.59
Weight loss	40 301 (26.1)	39 803 (25.8)	.48
Elixhauser comorbid conditions, total No.			
Mean (SD)	4.4 (2.5)	4.3 (2.3)	.05
Median (IQR)	4 (3–6)	4 (3–6)	
Discharge diagnoses, No.			
Mean (SD)	14.3 (6.6)	17.5 (6.3)	<.001
Median (IQR)	14 (9–18)	17 (13–23)	
Procedures, No.			
Mean (SD)	2.9 (3.2)	4.5 (4.5)	<.001
Median (IQR)	2 (1–4)	3 (1–6)	
Abdominal procedures/ operations	6084 (3.9)	6335 (4.1)	.32
Hospital characteristics			
Census region			
Northeast	28 080 (18.2)	28 761 (18.7)	
Midwest	31 179 (20.2)	31 817 (20.7)	.72
West	63 478 (41.1)	62 151 (40.3)	
South	31 594 (20.5)	31 317 (20.3)	
Location/teaching status			
Rural	9817 (6.4)	10 152 (6.6)	
Urban nonteaching	53 367 (34.6)	52 016 (33.8)	.38
Urban teaching	91 002 (59.0)	91 913 (59.7)	
Hospital size			
Small (1–49 beds)	16 480 (10.7)	15 168 (9.8)	
Medium (50–99 beds)	32 986 (21.4)	32 689 (21.2)	.10
Large (≥100 beds)	104 720 (67.9)	106 224 (68.9)	
Hospital IA caseload, %[e]			
Mean (SD)	0.3 (0.3)	0.5 (0.8)	…
Median (IQR)	0.2 (0.1–0.4)	0.4 (0.2–0.6)	<.001

Since the distributions were non-normal, the appropriate comparison values are provided for the median but not the mean values.

Abbreviations: HIV, human immunodeficiency virus; IA, invasive aspergillosis; IQR, interquartile range; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]The Agency for Healthcare Research and Quality prohibits reporting on <10 cases.

[c]Includes pneumonia, chronic obstructive pulmonary disease, and HIV infection.

[d]Total adds up to >100% because it is possible to have >1 comorbid condition per discharge.

[e]Factor not matched on because it was defined based on the exposure of interest.

Table 4. Propensity-Adjusted Hospital Outcomes

Outcome	Non-IA Group (n = 154 186)	IA Group (n = 154 081)	*P* Value
Mortality rate, No. (%)	15 902 (10.3)	21 748 (14.1)	<.001
Length of stay, d			
Mean (SD)	11.8 (15.6)	17.9 (20.1)	
Median (IQR)	7 (4–15)	12 (6–24)	<.001
Total charges, $			
Mean (SD)	126 385 (204 977)	185 529 (287 276)	
Median (IQR)	59 831 (27 503–139 724)	92 048 (40 354–215 034)	<.001
Total costs, $			
Mean (SD)	35 038 (53 301)	50 519 (73 716)	
Median (IQR)	17 134 (8555–38 962)	25 836 (12 177–59 880)	<.001

Abbreviations: IA, invasive aspergillosis; IQR, interquartile range; SD, standard deviation.

with chronic care facility or home health care. Given advances in the continuum of healthcare delivery since 1996, it is likely that some of the expenditures in the older estimates include the chronic care days that are missing from the current acute-care data set.

Sixth, it is not possible to differentiate in the NIS database initial versus repeated hospitalization. Because the patients who require readmission may differ systematically from those who do not, this may be a source of potential bias. However, given that SID analyses, in which readmissions can be differentiated from index hospitalizations, broadly confirmed the associations noted in the NIS data, this is not likely to present a significant threat to validity. Finally, as in any cohort study, residual confounding is a risk due to unmeasured variables not found in this database, although our propensity scores were based on a large number of covariates.

In summary, although rare even among high-risk groups, IA is associated with high hospital mortality rates, excess duration of hospitalization, and a 40% relative increase in the odds of 30-day readmission. Given nearly 40 000 annual IA admissions in the United States, at an excess cost of $15 000, the aggregate IA-attributable excess costs in the United States may reach $600 million annually.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. D. Z., R. H., J. R. S., and A. F. S. contributed substantially to the study design, data interpretation, and the writing of the manuscript. B. H. N. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; he contributed substantially to the study design, data interpretation, and the writing of the manuscript. No one other than the listed authors participated in the study design, analysis, interpretation or manuscript drafting. M. D. Z. takes responsibility for the content of the manuscript, including the data and analysis.

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