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Clinical characteristics and mortality of hospitalized alcoholic hepatitis patients in the United States

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Abstract

Background and aims—Alcoholic hepatitis (AH) is the most florid manifestation of alcoholic liver disease. In this study, we examined the clinical characteristics and risk factors associated with mortality in hospitalized alcoholic hepatitis patients in the United States using the 2007 Nationwide inpatient sample of the Healthcare Cost and Utilization Project.

Methods—Patients who were hospitalized with the primary diagnosis of alcoholic hepatitis in the United States in 2007 were identified using ICD-9 code. We further characterized these subjects based on associated symptoms (such as ascites, hepatic encephalopathy, and coagulopathy), complications during hospitalization (such as sepsis, pneumonia, spontaneous bacterial peritonitis, acute renal failure, as well as categories pertaining to hospital characteristics, such teaching status. The predictors of mortality were calculated using logistic regression analyses.

Results—There were 8,043,415 inpatient admissions, of which 56,809 (0.71%) were hospitalized with the primary diagnosis of AH. The mean age was 53.2 years, and 27% were female. The average length of stay (LOS) was 6.5 ± 7.7 days and 3,881 subjects (6.8%) died during hospitalization. Medicare and Medicaid were the main primary expected payer sources (51.8%) with the average total charges during hospital stay of $37,769. In the multivariate analyses, older age, presence of sepsis, spontaneous bacterial peritonitis, pneumonia, urinary tract infection, acute renal failure, hepatic encephalopathy and coagulopathy were independently associated with inpatient mortality.

Conclusion—In-hospital mortality rate for AH remains high, especially in those with infectious complications, hepatic encephalopathy, coagulopathy, and acute renal failure. Our analysis documented significant healthcare cost and utilization among hospitalized AH patients.

Keywords

Alcoholic hepatitis; in-hospital mortality; NIS data

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INTRODUCTION

Alcoholic hepatitis (AH) is an acute hepatic inflammation associated with significant morbidity and mortality that occurs in a subset of patients that consume excessive amounts of alcohol (1). In mild cases, patients may improve and have a favorable outcome with conservative management and alcohol abstinence. Those with more severe cases of AH; however, have a high mortality rate. Several clinical models have been developed over the past years trying to predict mortality and optimize strategies to prognosticate patients with AH. The Maddrey discriminant function (DF); which was introduced in the late 1970s, is used widely as a clinical tool to predict risk of 30-day mortality and identify a subset of patients that may benefit from intervention with corticosteroids (2). The model for end-stage liver disease (MELD) is a survival model based on a composite of three laboratory variables: serum creatinine, serum bilirubin, and international normalized ratio (INR) for PT. When using the appropriate cutoff, MELD model is very useful and accurately predict 30- and 90-day mortality in patients with AH (3). Aside from the laboratory-derived model, physical examination signs of encephalopathy and ascites may be useful as a quick bedside screening test for mortality. Hospitalized AH patients in the absence of these two physical signs tend to have a better clinical outcome and survive at 90-day follow up (3). In this study, we examined the clinical characteristics and risk factors associated with inpatient mortality in AH cases who were hospitalized in the United States. We also explored the association between inpatient mortality and several categories pertaining to hospital characteristics, such teaching hospital status, locations, and support personnel.

METHODS

Data source

We extracted the data from the 2007 National Inpatient Sample (NIS). The NIS is the largest all-payer inpatient care database containing data from 5 to 8 million hospital stays from about 1,000 hospitals in the United States. These data are collected as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ) (4). The NIS is designed to approximate a 20-percent sample of U.S. non-federal hospitals, including public hospitals and academic medical centers assigned by the American Hospital Association. In 2007, dataset also includes long term acute care facilities which provide acute care services to patients who need long term hospitalization (stays of more than 25 days). Short-term rehabilitation hospitals, long-term non-acute care hospitals, psychiatric hospitals, and alcoholism/chemical dependency treatment centers were not part of the data collection.

Each hospital record includes a unique patient identifier, demographic data, admission type, primary and secondary diagnosis and procedures, primary and secondary insurance payers, length of stay including hospital charges, and hospital characteristics. Hospital *g*eographic region was sub-categorized into Northeast, Midwest, West, and South The control/ ownership of the hospitals were classified as government non-Federal (public), private not-for-profit (voluntary), and private investor-owned (proprietary). Teaching hospitals are those with any one of the following three criteria; i) residency training approval by the Accreditation Council for Graduate Medical Education, 2) membership in the Council of Teaching Hospitals, and 3) a ratio of full-time equivalent interns and residents to beds of .25 or higher.

Cases and outcome variables identification

We used Clinical Modification of the International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes to capture all admissions in the NIS dataset with the

primary diagnosis of alcoholic hepatitis (AH, 571.1). The following ICD-9 codes were also used; hepatitis C infection (070.70, 070.44, and 070.54), hepatitis B infection (070.3), cirrhosis (571.5), ascites (789.5), hepatic encephalopathy (572.2), coagulopathy (286.7 and 286.9), and acute renal failure (584.50, 584.90, 586.00, and 593.90). Because the primary outcome of this study was the in-hospital death from AH, we also identified infectious complications during hospital stay, a well known mortality risk factor in AH patients. These included sepsis (38.00–38.90), pneumonia (481.00–483.00), spontaneous bacterial peritonitis (567.23), and urinary tract infection (599.00).

Statistical analyses

Data were analyzed using the SAS statistical software (SAS Institute, Cary, NC). Basic descriptive statistics, including means, standard deviations (SD), and percentages, were used to characterize the study patients. Comparisons between groups were made using Student's t test for the continuous and chi-square, χ^2 analyses for the categorical variables.

The primary outcome of interest for this study was the in-hospital mortality. All hospitalized AH patients were dichotomized into two groups, those who died during the hospitalization and those who survived. Comparisons between these two groups were made using Student's t test for the continuous and chi-square, χ^2 analyses for the categorical variables (Table 4). The evaluation of independent predictors of mortality was further carried out using logistic regression analyses, odd ratios (OR) and its corresponding confidence intervals (CI) (Table 5). We anticipated that there might be a strong relationship between certain variables, especially in the infectious complication categories (sepsis, SBP, UTI, and pneumonia). For instance in clinical settings, sepsis might be secondary to underlying SBP or UTI. Unfortunately, the NIS dataset does not allow us to determine the causality. We used Cohen's Kappa (κ) coefficient to measure the agreement between these variables and found the very poor agreement between these variables; sepsis vs. SBP ($\kappa = 0.03$), sepsis vs. pneumonia ($\kappa = 0.05$), sepsis vs. UTI ($\kappa = 0.08$), and SBP vs. UTI ($\kappa = 0.008$). Therefore, these variables were entered separately in the multivariate model. A p value less than 0.05 was considered statistically significant.

RESULTS

Baseline demographics and clinical characteristics of hospitalized AH

The number of hospitalizations in the Unites States in 2007 was 8,043,415. Of these, 56,809 (0.71%) were admitted with the diagnosis of AH. The mean age of these patients was 53.2 ± 11.4 yrs and 66.3% were White. There was a greater male predominance among hospitalized patients (73.2 vs. 26.8, $p < 0.001$). When using the household income national quartile as the measurement of socioeconomic status, 32% were in the first quartile (annual family income < $36,539); whereas 18% were in the top (fourth) quartile (annual family income ≥ $98,434). Most patients were admitted directly from the emergency department and only 19.7% were seen in outpatient clinics and then hospitalized. The overall inpatient mortality, defined as those who died during hospitalization, was 6.8%. The average length of stay (LOS) was 6.5 days and the majority of patients (62.6%) can be discharged directly to home, 7.8% to skilled nursing facility, 7.5% to home healthcare, and 2.4% to hospice care. Medicare (28.3%) and Medicaid (23.5%) were the major primary payers. The average total charges during hospitalization for AH were $37,769 or $6,248/day when adjusted for LOS. The detailed characteristics of these patients were shown in Table 1.

Characteristics of hospitals and healthcare facility

The majority of cases (61.1%) were hospitalized in the government or privately-owned hospitals. Patients primarily lived in the urban area (89.2%) and 35% resided in the South.

Forty seven percent of patients were in the teaching hospital. Other hospital characteristics were shown in Table 2.

Signs, symptoms, co-morbidities and complications of hospitalized AH patients

We further characterized clinical presentations of hospitalized AH patients (Table 3). At the time of admission, 13.7% presented with ascites alone, 10.5% with hepatic encephalopathy, and 4.8% with coagulopathy. Approximately 2.3%–4.6% had 2 clinical presentations (such as ascites and hepatic encephalopathy, or ascites and coagulopathy). Only 1.5% of patients presented with all three clinical symptoms. Other common infectious complications related to admission were urinary tract infection (UTI, 9.7%), sepsis (2.2%), and spontaneous bacterial peritonitis (2.1%). Nineteen percent of AH patients had coexistent hepatitis C infection and none had chronic hepatitis B infection. Acute renal failure was found in 20% during the hospital stay.

Clinical characteristics and predictors of in-hospital mortality

As stated earlier, the overall in-hospital mortality rate among admissions for AH was 6.8%. Case fatality was higher among older patients, and this was still statistically significant after multivariate adjustments (adjusted odd ratios, OR 1.02 [95% CI 1.01–1.02]). There were no differences in in-hospital deaths among those with or without coexistent HCV infections (18.6% vs. 19.5%, $p = 0.16$), and those with or without cirrhosis (1.1 vs. 0.9, $p = 0.29$). The prevalence of infectious complications was significantly higher in fatality cases when compared to those who survived (*for example*, sepsis 7.3% vs. 1.8%, $p < 0.001$, SBP 5.4% vs. 1.8%, $p < 0.001$, UTI 12.9% vs. 9.5%, $p < 0.001$, and pneumonia 1.3% vs. 0.3%, $p < 0.001$). Each infectious complication was independently associated with in-hospital mortality in the multivariate logistic regression analyses. Approximately 56% of cases who died developed acute renal failure, compared to only 17% in non-fatality cases ($p < 0.001$) and its presence was strongly associated with in-patient mortality (OR 4.54 [95% CI 4.21–4.89]). When we analyzed the association between the physical examination signs and mortality, we found that the presence of encephalopathy (OR 1.95 [95% CI 1.81–2.1]), coagulopathy (OR 2.87 [95% CI 2.64–3.14]), and ascites (OR 1.24 [95% CI 1.14–1.35] were associated with in-hospital death in AH patients after adjusting for other comorbidities. The detailed characteristics and results were shown in Tables 4 and 5.

Healthcare Utilization

LOS was substantially higher among those who died compared to those who survived (9.3 days vs. 6.2 days). Average total charges and total charges per day were ~ 2.5-fold and ~ 2-fold higher, respectively, for those who died compared to those who did not ($84,642 vs. $34,343, $p < 0.001$ and $11,754 vs. 5,862, $p < 0.001$) (Table 4). The mortality rate in those who were hospitalized in the teaching hospital was less than that in non-teaching facility (48.7% vs. 52.8%, Table 4). Case fatality was higher among hospitalized patients in facility with higher licensed practical nurse full time employees (LPN FTEs), nurse aids, and registered nurse FTEs; however, these variables were no longer statistically significant after multivariate adjustment for other factors (Table 5).

DISCUSSION

To the best of our knowledge, this is the first study to report the clinical characteristics and risk factors for in-hospital mortality from AH using the large population-based NIS data. Our study makes some important observations. We found the high in-hospital mortality rate among patients who were hospitalized for AH. In 2007, alcoholic hepatitis accounted for 0.71% of overall admissions in the United States (~706/100,000 for all admissions) with the in-hospital mortality rate of 6.8% (~6,831/100,000 for all hospitalized AH patients). Such

rate is higher than the overall mortality from alcoholic liver disease (4.4/100,000) and from hepatitis C infection (2.9/100,000), emphasizing the severity of this florid manifestation of alcohol-induced liver injury (5). Women are more susceptible than men to the adverse effects of alcohol and they develop AH after a shorter period and smaller amounts of alcohol abuse than men (1). We, however, observed significantly higher proportion of male in hospitalized AH patients. This finding is not surprising given that more men drink alcohol above the 'safety range' than women (1). In general, the overall mortality rates of AH have consistently been far greater for the nonwhite than the white population (5). We found no racial differences in in-hospital mortality. This result needs to be cautiously interpreted. First, our data are only applicable to hospitalized fatality cases. Second, NIS data that do not allow us to track the cases beyond the hospital stay, thus it limits our ability to calculate the overall short and long term mortalities.

The impact of hepatitis C virus on the outcome of AH remains debatable. Hepatitis C can cause oxidative stress, lipid peroxidation, and reduce intrahepatic glutathione (6). The consequences of alcohol-induced liver injury also lead to similar alterations, suggesting the possible synergistic interactions and worsening outcomes of hepatitis C-infected AH patients (6). We did not find the difference in the prevalence of hepatitis C infection in those who died and survived during the hospital stay. In addition, the mortality was not influenced by the presence of underlying cirrhosis. We, however, must vigilantly interpret these observations. First we used the ICD-9 codes for the identification of hepatitis C and cirrhosis and such method might not completely identify all patients. Second, NIS dataset does not include laboratory and radiographic data; therefore, we cannot exclude the possibility that we might underestimate the true prevalence of hepatitis C and cirrhosis in our study cohort. Lastly, as mentioned above, the results are only pertinent to the in-hospital mortality risk. Because of these shortcomings, our study cannot appropriately address the actual impact of hepatitis C on the outcome of AH.

We found the significant increase in mortality of AH patients who developed infections (i.e. sepsis or SBP) during the hospital stay. Additionally, we also found that the presence of hepatic encephalopathy, coagulopathy, and ascites were strongly associated with mortality. These clinical signs are the measures of severity of liver injury, and undoubtedly, once present, related with high mortality in AH patients. In accordance with the study by Dunn et al.(3), we also found presence of ascites as the predictor of mortality. The strongest predictor associated with mortality in hospitalized AH patients was the presence of acute renal failure. The presence of acute renal failure in conjunction with coagulopathy is the basis of the model for end-stage liver disease (MELD). Thus it emphasizes the usefulness of utilizing this model clinically to determine the prognosis and mortality risks of hospitalized AH patients.

Hospitalized AH patients result in significant healthcare cost and utilization. Patients with AH were hospitalized in different geographic locations especially in the urban areas. We found that federal (Medicare) or state (Medicaid) supported health insurance program is the main primary expected payer. This finding was compatible with the levels of socioeconomic status which was measured by household income national quartile of the study cohort. The average total charges during hospitalization for AH were $37,769; which was higher than that from acute myocardial infarction (~$16,200), acute cerebrovascular disease (~$11,100), and acute pancreatitis ($9,870) (7;8). Costs per hospitalization and cost adjusted for LOS were higher in those who died during the hospital stay, presumably from more severe forms of AH ($84,642 and $11,754/day, respectively). Early intervention and prevention to promote alcohol abstinence, thus prevent the episode of AH among abusive drinkers are essential to reduce the in-hospital related healthcare costs.

In those who died, 48% were admitted into teaching hospital and 51% were in the non-teaching hospital. However, in the multivariate logistic regression analyses controlling for co-morbidities, nursing supports and personnel, the status of the teaching hospital was not associated with in-hospital mortality. The rationale of this finding is not quite clear. These patients might benefit from the presence of sub-specialists, multidisciplinary teams, and adjunctive clinical resources in the teaching institutions (9); however, it is plausible that patients who were hospitalized in the teaching hospital tend to be sicker and more complicated; leading to unfavorable outcome (9). Further studies are needed to determine the association between teaching/non teaching hospitals and mortality risk of hospitalized AH patients.

This study has a few potential limitations. First, our analysis may be limited by the accuracy of the HCUP Nationwide Inpatient Sample database, which is based on medical record coding (10;11). Second, we also acknowledge the deficiencies of using ICD-9 codes to identify the diagnosis of alcoholic hepatitis and certain physical signs and symptoms which might lead to underestimation of cases. For instance, the ICD-9 codes might not identify all patients with cirrhosis (11). Third, the NIS dataset does not provide laboratory, microbiology, or radiographic data that can be linked and confirmed the presence or absence of specific clinical presentations such as coagulopathy or infectious complications. Fourth, several clinical scoring systems, such as Child-Turcotte-Pugh score (12), the Maddrey discriminant function (2), the MELD scores (3), and the Glasgow alcoholic hepatitis scores (13) have been derived to predict the clinical outcome of patients with AH. Because of the limitation in NIS dataset, we are unable to specifically characterize AH subjects based on this scoring system. Lastly, our results are relevant to *in-hospital mortality* only as we do not have specific outcomes or mortality data of patients once they were discharged from the hospitals. Despite these shortcomings, our study is strengthened by the use of a database that represents a wide variety of U.S. medical centers and patient populations. The NIS dataset also allowed us to determine the healthcare cost and utilization of patients with AH.

In conclusions, in-hospital mortality rate for AH remains high, especially in those with infectious complications, hepatic encephalopathy, coagulopathy, ascites, and acute renal failure. Our analysis documented significant healthcare cost and utilization among hospitalized AH patients. These results should serve as a catalyst for better screening, education, and interventions among abusive drinkers aimed at promoting alcohol abstinence, thus preventing episodes of AH.

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Table 1

Demographic and clinical characteristics of 56,809 hospitalized alcoholic hepatitis subjects in the United States in 2007

Variable	Value
Age (Yrs ± SD)	53.2 ± 11.4
Race (%)	
- White	66.3
- Black	10.9
- Hispanic	17.7
- Others	5.1
Gender (Female,%)	26.8
Median household income national quartile	
- First quartile	32.2
- Second quartile	26.9
- Third quartile	22.8
- Fourth quartile	18.1
Admission Source (%)	
- Emergency Department	74.9
- Routine outpatient clinic	19.7
- Other healthcare facility (i.e., long term care)	1.4
- Another hospital referral	4
Weekend admission (%)	22.7
Died during hospitalization (N, %)	3,881 (6.8)
Patient disposition (%)	
- Routine discharge to home	62.6
- Skilled nursing facility	7.8
- Home healthcare	7.5
- Against medical advice	3.8
- Short-term hospital	2.9
- Hospice	2.4
- Others (such as rehabilitation hospital, nursing facility certified under Medicaid but not Medicare, Long term care hospital)	13
Length of hospital stay (LOS, days) (mean ± SD)	6.5 ± 7.7
Primary expected payer (%)	
- Medicare	28.3
- Medicaid	23.5
- Private insurance	25.6
- Self pay	14.7

Variable	Value
- Others	7.9
Secondary expected payer (%)	
- Medicare	14.2
- Medicaid	28.8
- Private insurance	21.5
- Self pay	27.5
- Others	8
Total charges during hospitalization in US dollars ($) (mean ± SD)	37,769 ± 63,598
Average total charges adjusted by LOS ($/day) (mean ± SD)	6,248 ± 6,486

Table 2

Admitting hospital locations and characteristics

Variable	value
Control/ownership of admitting hospital (%)	
- Government or private	61.1
- Government, non-federal	6.5
- Private, not for profit	19.5
- Others	12.9
Region of admitting hospital (%)	
- Northeast	17.4
- Midwest	20.0
- South	35.5
- West	27.1
Hospital location (%)	
- Rural	10.8
- Urban	89.2
Teaching status of the hospital (%)	
- Non teaching	52.7
- Teaching	47.2
LPN FTEs per 1000 adjusted patient days (mean ± SD)	0.35 ± 0.34
Nurse aids per 1000 adjusted patient days (mean ± SD)	0.93 ± 0.52
RN FTEs per 1000 adjusted patient days (mean ± SD)	3.91 ± 1.32
Percentage of RN among licensed nurses	91.4 ± 7.5

Table 3

Sign, symptoms, infections, and co-morbidities at the time of admission or during hospital stay in hospitalized alcoholic hepatitis subjects

Variable	value
Signs and symptoms (N, %)	
- Ascites	7,766 (13.7)
- Hepatic encephalopathy	5,945 (10.5)
- Coagulopathy	2,714 (4.8)
- Ascites + hepatic encephalopathy	2,643 (4.6)
- Ascites + coagulopathy	1,462 (2.6)
- Hepatic encephalopathy + coagulopathy	1,298 (2.3)
- Ascites + Hepatic encephalopathy + coagulopathy	868 (1.5)
Infections (N, %)	
- Sepsis	1,222 (2.2)
- Pneumonia	234 (0.4)
- Spontaneous bacterial peritonitis	1,172 (2.1)
- Urinary tract infection	5,507 (9.7)
Other co-morbidities (N, %)	
- Underlying hepatitis C infection	11,071 (19.5)
- Presence of cirrhosis	553 (0.97)
- Acute renal failure	11,384 (20.0)

Table 4

Characteristics of alcoholic hepatitis subjects who died during hospitalization and those who survived according to univariate analysis

Variable	Subjects who died during hospitalization (n = 3,881)	Subjects who survived during hospitalization (n = 52,928)	p-value
Age (mean ± SD)	52.9 ± 11.4	55.9 ± 11.1	< 0.001
Race (%)			0.12
- White	66.6	66.3	
- Black	11.3	10.9	
- Hispanic	17.6	17.7	
- Others	4.5	5.1	
Gender (female, %)	25.0	26.9	0.01
Presence of hepatitis C	18.6	19.5	0.16
Presence of cirrhosis	1.1	0.9	0.29
Sepsis	7.3	1.8	<0.001
Pneumonia	1.3	0.3	<0.001
Spontaneous bacterial peritonitis	5.4	1.8	<0.001
Urinary tract infection	12.9	9.5	<0.001
Acute renal failure	56.2	17.4	<0.001
Presence of ascites	12.9	13.7	0.19
Presence of hepatic encephalopathy	15.4	10.1	<0.001
Presence of coagulopathy	11.3	4.3	<0.001
Length of stay (days) (mean ± SD)	9.3 ± 10.8	6.2 ± 7.4	<0.001
Teaching status of the hospital (%)			0.04
- Non teaching hospital	51.3	52.8	
- Teaching hospital	48.7	47.2	
LPN FTEs per 1000 adjusted patient days (mean ± SD)	0.36 ± 0.35	0.35 ± 0.34	0.006
Nurse aids per 1000 adjusted patient days (mean ± SD)	0.97 ± 0.51	0.93 ± 0.53	0.004
RN FTEs per 1000 adjusted patient days (mean ± SD)	4.0 ± 1.4	3.9 ± 1.3	<0.001
Total charges during hospitalization in US dollars ($) (mean± SD)	84,642 ± 121,889	34,343 ± 55,529	<0.001
Average total charges adjusted by LOS ($/day) (mean± SD)	11,754 ± 13,725	5,862 ± 5,436	<0.001

Table 5

Univariate and multivariate logistic regression analyses of predictors for inpatient mortality in alcoholic hepatitis subjects

Variable	Univariate analyses			Multivariate analyses		
	Odd ratios	95% CI	p-value	Odd ratios	95% CI	p-value
Age	1.023	1.020–1.025	<0.001	1.02	1.01–1.019	<0.001
Race	1.028	0.912–1.16	0.06	*n/a*		
Gender (female)	0.91	0.84–0.97	0.01	0.92	0.84–1.00	0.06
Presence of hepatitis C	0.94	0.86–1.02	0.16	*n/a*		
Presence of cirrhosis	1.18	0.86–1.60	0.29	*n/a*		
Sepsis	4.33	3.77–4.96	<0.001	2.78	2.36–3.27	<0.001
Pneumonia	3.84	2.81–5.24	<0.001	3.16	2.21–4.51	<0.001
Spontaneous bacterial peritonitis	3.11	2.67–3.62	<0.001	1.64	1.36–1.96	<0.001
Urinary tract infection	1.42	1.28–1.56	<0.001	1.32	1.26–1.96	0.05
Acute renal failure	6.09	5.69–6.52	<0.001	4.54	4.21–4.89	<0.001
Presence of ascites	1.84	1.72–1.97	<0.001	1.24	1.14–1.35	0.001
Presence of hepatic encephalopathy	2.89	2.70–3.10	<0.001	1.95	1.81–2.11	<0.001
Presence of coagulopathy	3.66	3.40–9.94	<0.001	2.87	2.64–3.14	<0.001
Teaching status of the hospital (teaching vs. non-teaching)	1.06	0.99–1.13	0.07	*n/a*		
LPN FTEs per 1000 adjusted patient days	1.14	1.03–1.24	0.001	1.09	*0.98–1.24*	*0.20*
Nurse aids per 1000 adjusted patient days	1.12	1.05–1.19	<0.001	1.06	0.98–1.14	0.11
RN FTEs per 1000 adjusted patient days	1.06	1.03–1.08	<0.001	1.01	0.98–1.04	0.45