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The Burden and Trend of Paget's Disease Among Hospitalized Patients in the United States

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Abstract: Objective: To assess characteristics of inpatient mortality and morbidity associated with Paget's disease in the United States from 2001-2010. Methods: This retrospective cohort study of hospital inpatients diagnosed with Paget's disease utilized Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project and Nationwide Inpatient Sample data from 2001-2010. Patients were included if they were ⩾ 18 years with diagnosis of Paget's disease. Analysis variables included patient demographics, hospital characteristics, length of stay, primary payer and clinical comorbidities. Outcomes were assessed via multivariate logistic and gamma regression yielding odds ratios or exponentiated beta coefficients. Results: Overall, 144,869 Paget's disease cases were identified. Average age was 80.01 (±10.78) years with average length of stay 5.5 (±5.83) days. There were 49% male and 51% female patients. Mortality occurred in 2.9% of all Paget's disease hospitalizations, although there was decreasing trends for both mortality and total charges associated with Paget's disease hospitalization. Multivariate analysis indicated significantly higher inpatient mortality for age, large bed-size hospital, and cases with primary payer of Tricare or other government program. Adjusted for age, comorbidities associated with increased mortality and total inpatient charges were heart failure, coagulopathy, electrolytes disorders, metastatic cancer, neurological disorders, paralysis, renal failure and weight loss. Conclusion: Although mortality from Paget's disease decreased form 2001-2010, increased mortality and total hospital charges were associated with co-presence of severe morbidities. Increased understanding of these morbidities remains essential to improve treatment and patient outcomes.

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1. Introduction

In 1877, James Paget was the first to describe "osteitis deformans" in an elderly man with progressive skeletal deformities. The condition afterward became known as Paget's Disease of Bone (PDB). Rapid bone remodeling with formation of abnormal bone are the main characteristic of Paget's disease1. The etiology of Paget's disease still unknown, while there are some theories implicating both genetic and environmental factors[1]. Bone deformity and enlargement can affect both single or multiple bones while the most frequently involved bone are the skull, long bones, clavicles, and vertebral bodies[3]. Moreover it is a highly localized disease and it is rare to develop new lesions during the disease course [3]. The jaws are affected in around 15% of the cases and the most common dental complications for PDB are malocclusion, tooth mobility, root resorption, hypercementosis and excessive bleeding on extraction [11]. Incidence is more common in the maxilla by a 2:1 ratio to the mandible [11].

In England, a study was done called the General Practice Research Database (GPRD) studied the prevalence and incidence of Paget's disease from 1988 to 1999 among 5 million subjects who were 18 years old and older1. The information recorded included diagnosis and treatment and they found that there were 2465 Paget's patients among their subjects[1]. Moreover, the incidence rate among 55-59 years old subjects ranged from 0.3-0.5/10,000 cases. Also, the incidence rate ranged from 5.4-7.6/10,000 cases among the 85 years old group and older [1]. Another study was done by Barker et al, in 1980 studied Paget's disease prevalence in the British hospitals from 1970 to 1977 had around 30,000 subjects [8]. They included in this study subjects who were 55 years old and older in both genders and they used radiographs to confirm the diagnosis [8].

The study reported that 5% of their sample had Paget's disease 8. In 1984, Barker et al, did another study about Paget's disease prevalence but this one was in the United States [6]. The study compared between the prevalence of Paget's disease in northern city, New York, with a southern city, Atlanta to compare between the two major ethnic groups (black and white) and the study excluded all other ethnic groups [6]. They analyzed 4726 radiograph and the result was that there were 3.9% Paget's disease patients among their sample in New York compared to 0.9% in Atlanta [6]. Bastin et al, also did a study in 2009 in New Zealand to study the prevalence of Paget's disease from 2005-2006 [12]. They analyzed 3350 plain abdominal radiographs for subjects who were 54 years old and older [12]. The total prevalence of Paget's disease was 2.6% in the overall sample while it was 2% among female and 3% among male patients[12].

Paget's disease of bone (PDB) affects 2–3% of the population over the age of 60 with very unusual geographic distribution through an increased incidence in Caucasians of European descent, but it also arises in African Americans and South Americans while it is very rare in Asian [3, 9]. PDB shows a strong age-dependency; it is uncommonly diagnosed below the age of 50 while they usually diagnosed in the sixth decade but becomes increasingly more common afterward reaching 15% in elderly men in Britain[1, 7]. A study was done by Barker in 1980 reported an increase in the frequency of Paget's disease with progressing in age in both genders. Therefore, the prevalence rose from 2% among men aged 55–59 years to 20% in those aged 85 years. Moreover, the prevalence in women for the same age groups rose from 1% to around 7%8. PDB affects about 8% of men and 5% of women in the United Kingdom by the age of 80 which also was confirmed by postmortem and radiographic imaging[1,4,7]. The unique geographic distribution of Paget's disease was shown through the literature (table 2). Many studies reported high prevalence rates of radiographic Paget's disease in Britain, New Zealand, South Africa, Australia, and North America. It is uncommon in Scandinavia and Western Europe while it is extremely rare in India and southern Asia[3,7]. Recently, countries with higher incidence rates of PDB reported a decline in the frequency of the condition. In Italy the data showed a decreased in the clinical severity of PDB with respect to other populations, which confirmed the familial aggregation of Paget's disease [16]. In New Zealand, there was a decline in the severity of Paget's disease cases in the last 40 years while the number of anatomical sites had increased in the proportion of monostotic lesions from 24% to 36%[2]. Mortality from Paget's disease among whites in the USA seems to show a similar pattern of decline [6]. Although Paget's disease is often asymptomatic disorder, its high prevalence makes it a significant cause of morbidity in the elderly [6].

Paget's Disease patients frequently are asymptomatic and only 10-15% experience increased morbidity through severe symptoms including bone pain, fractures, neurological complications from spinal cord compression, deafness due to skull enlargement, and dental abnormalities [1, 3, 4]. Fractures are the most common comorbidity associated with Paget's Disease patients. In the GPRD study, Paget's Disease patients were 1.2 times more likely to experience a fracture than non-Paget's disease patients[1]. Moreover in the study by Tiegs et al., there were 11% fractures reported in the medical records among Paget's Disease patients from 1950 through 1994, [15]. Bone pain was the second most common comorbidity associated with Paget's Disease patients. Tiegs et al, study found that bone pain was reported from 32% of patients 15 while Merlotti et al, study found that 38.8% of Paget's Disease patients had bone pain 19. Osteoarthritis was also one of the comorbidities investigated among Paget's Disease patients. The GPRD study reported that the relative risk for osteoarthritis among Paget's Disease patients was 1.7 [1]. The Merlotti et al, study reported that 45.57% of Paget's Disease patients suffered from osteoarthritis 19 while Siris study reported osteoarthritis among 64% of the patients [17]. Other comorbid conditions reported were hearing loss, headache and osteoporosis [1,15,19].

The treatment of Paget's disease aims toward controlling the disease progression and managing its complications. Asymptomatic Paget's disease with normal serum alkaline phosphatase requires no treatment while Paget's Disease patients with bone pain can take anti-inflammatory drugs or pain-relieving medications [14]. Damaged joints, fractures and severe bone deformity may require surgical operation. The medical treatment of symptomatic Paget's disease involves either bisphosphonates or injectable calcitonin[14]. These medications effectively reduce bone remodeling as evaluated by biochemical markers[14]. The use of nitrogenated bisphosphonates (alendronate, risedronate, pamidronate, and zoledronic acid) is indicated for the treatment of Paget's disease, emphasizing that zoledronic acid is the most potent bisphosphonate. (Diagnosis and management of Paget's disease of bone) for use with this disease.

The purpose of this study to was to analyze data from a national database to determine the inpatient characteristics of Paget's disease of the bone patients in the United States from 2001-2014 and to investigate previous studies that have been published

regarding the trend and epidemiology of Paget's disease in the United States and worldwide.

2. Methods

This study was a retrospective, inpatient burden of illness investigation utilizing a nationally representative sample of hospital discharges for Paget's disease in the United States. Inpatient discharge records from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP), Nationwide Inpatient Sample (NIS) from 2001-2010 were used. This database is the largest all-payer inpatient care database in the United States, containing data on more than seven million hospital stays from approximately 1,000 hospitals. This ideal sample size is perfect for creating national and regional estimates and enables analyses of rare conditions, uncommon treatments, and special populations. The database includes information on patient demographics, diagnoses, procedures, admission and discharge characteristics, payer status, hospital characteristics, total discharges, and length of stay. NIS contains all discharge data from 1,045 hospitals located in 46 States, approximating a 20-percent stratified sample of U.S. community hospitals.

The inclusion criteria for this analysis were hospitalized patient, 18 years and older with mention of discharge diagnosis or associated diagnoses of ICD-9 code (731.0) Osteitis deformans without mention of bone tumor (Paget's disease of bone). To ensure maximum representation of hospitals in the United States, the following sampling strata based on five important hospital characteristics were employed for the creation of the NIS: geographic region, ownership, location, teaching status and size in terms of number of beds.

Two key outcomes were assessed in this study: 1) in-hospital mortality and 2) hospitalization inflation adjusted charges. In-hospital mortality was noted as one of the variables in the dataset. Hospitalization charges were derived by linking the Agency for Healthcare Research and Quality's (AHRQ) cost-to-charge ratio file to total charges within HCUP. Patient-specific covariates included age, gender, median income based on the patient's zip-code of residence as well as the expected primary payer (whether it was Medicare, Medicaid, private insurance, self-pay, no charges or other primary payer as Worker's Compensation,. Etc.). The region of the hospital was classified whether it was northeast, mid-west, south or west. Also, the analysis included the location whether it was rural or urban as well as the teaching status of the hospital. All of the patient and the hospital covariates were created within the HCUP database. The comorbidities were calculated using Elixhauser Comorbidity Index 23 and the list of specific ICD diagnosis codes that are used to identify different categories of comorbidity have been modified and updated from ICD-9-CM to work with ICD-10 coding [24].

A variable was defined to identify if this hospitalization was associated with trauma or not by using the New Injury Score (NISS), which considers the three most severe injuries, regardless of body region. The NISS is computed as the simple sum of squares of the three most severe abbreviated injury scale (AIS) (1990 revision) injuries[22]. The program used ICD-9-CM diagnosis codes to assign a severity score ranging from 1 to 75, with 75 being the most severe 22. The NISS score for Paget's Disease patients was retained in the HCUP data element. All statistical analyses were performed using the STATA version 12.0 statistical software. Demographic and clinical characteristics of Paget's Disease patients were evaluated using descriptive statistics including means, standard deviations, and proportions.

Patient, hospital factors and comorbidities associated with mortality were identified using Multivariate logistic regression to obtain odds ratios and 95% confidence intervals. The attributable burden of illness study model was built based on prior literature of Paget's Disease patients analyzing demographics, disease comorbidities as well as hospital setting associated with the disease. The relationships between Paget's Disease and hospital charges were evaluated using gamma regression to obtain exponentiated beta coefficients. For both analyses, the potential for effect modification of the associations by whether the hospitalization was associated with trauma was evaluated. We stratified the analysis by trauma and non-trauma related.

3. Results

Overall, findings indicated that 144,869 inpatient Paget's disease cases were observed from 2001-2010. Mortality occurred in 4,128 cases, constituting 2.9% of all Paget's disease hospitalizations. Demographic of the inpatient's cases appear in (Table 1). On average, cases were averaging 80.01 (±10.78) years of age and 5.5 (±5.83) days for length of stay. The majority of the cases were of white race 64.2% (79.5% of reported race) and there were 49% male and 51% female patients. The primary payer for the majority of the discharge was Medicare (87%). Hospital characteristics are summarized in (table 2). The majority of discharges were in larger hospitals (60.4%), in the northeast (34.4%), in nonteaching hospitals (54.9%) and in urban hospitals (87.2%). The prevalence of co-morbidities of Paget's disease inpatient and mortality cases appear in Table 3.

Table 1. Descriptive statistics for patient characteristics and primary payer of Paget's disease patients from 2001-2010

Patient Characteristics	*Frequency N=144,869*	*Percent (%)*
Age		
18-20	10	0.007
21-30	136	0.09
31-40	606	0.42
41-50	1949	1.34
51-60	6186	4.27
61-70	13689	9.45
71-80	39591	27.33
81-90	64365	44.43
91-100	18067	12.47
101-110	269	0.18
Sex		
Female	70805	48.9
Male	74059	51.1
Median household income by ZIP code		
$0-24,999	26514	18.3
$25,000-34,999	33868	23.4
$35,000-44,999	37055	25.6
$45,000+	45079	31.1
Missing	2353	1.6
Race		
White	93078	64.2%
Black	16016	11.1%
Hispanic	3538	2.4%
Asian	541	0.4%
Native American	244	0.2%
Other	1761	1.2%
Missing	29691	20.5%
Primary payer		
Medicare	126008	87.1%
Medicaid	2997	2.1%
Private insurance	13495	9.3%
Self-pay	862	0.6%
No charge	111	0.1%
Other	1253	0.9%
Missing	144	0.1%

Table 2. Hospital characteristics, hospital region and location of Paget's disease patients from 2001-2010

Hospital Characteristics	Frequency N= 144,869	Percent (%)
Hospital bed size		
Small	21079	14.6
Medium	36021	24.9
Large	87497	60.4
Missing	272	0.2
Hospital location		
Rural	18207	12.6
Urban	126391	87.2
Missing	272	0.2
Hospital teaching status		

Teaching	65105	54.9
Not teaching	79492	44.9
Missing	272	0.2
Hospital Region		
Northeast	49905	34.3
Midwest	41581	28.7
South	36848	25.4
West	16536	11.4
Missing	-	-

Comorbidities were associated with significantly higher mortality ($p < 0.05$) from the multivariate logistics regression. The overall inpatient mortality for Paget's disease patients were CHF (OR=1.99), coagulopathy (OR=1.60), hypertension (OR=0.65), hypothyroidism (OR=0.79), electrolyte disorder (OR=2.22), metastatic cancer (OR=2.19), neuropathy (OR=1.61), obesity (OR=0.41), paralysis (OR=2.02), renal failure (OR=1.98) and weight loss (OR=1.98). Hospital characteristics in terms of hospital region (Midwest (OR=0.69)) and (south (OR=0.79)) and hospital size (large (OR=1.28) were statistically significant with inpatient morality (table 4). The age (OR=1.05) of the cases as well as if they had primary payer other (OR=3.92) than Medicaid, Medicare, self-pay, no charge or private insurance were statistically significant with inpatient mortality. There was also a statistically significant association with the inpatient mortality from year 2005-2010. Then, we stratified the analysis by trauma and non-trauma related.

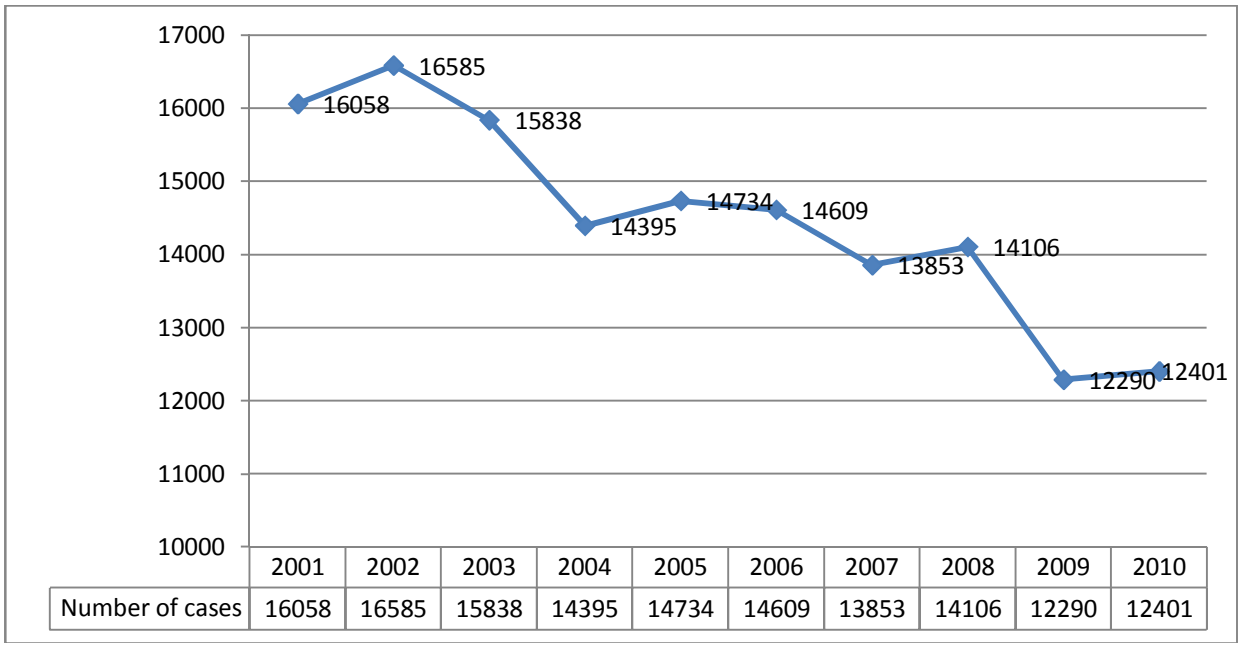
Table 3. AHRQ comorbid conditions among Paget's disease patients from 2001-2010

Co morbidity	**Frequency**	**Percent (%)**
AIDS	66	0.0
Alcohol Abuse	1412	1
Deficiency anemia	27881	19.6
Collagen vascular disease/RA	4486	3.1
Chronic blood loss anemia	2764	1.9
Congestive heart failure	18624	12.9
Chronic Pulmonary disease	26525	18.3
Coagulopathy	4040	2.8
Depression	12959	8.9
Diabetes uncomplicated	26113	18
Diabetes complicated	4768	3.3
Drug abuse	827	0.6
Hypertension	86679	59.8
Hypothyroidism	19230	13.3
Liver disease	1670	1.2
Lymphoma	1554	1.1
Electrolyte disorder	28981	20
Metastatic cancer	3178	2.2
Neurological disorder	13135	9.1
Obesity	5221	3.6
Paralysis	3535	2.4
Peripheral Vascular disorder	9907	6.8
psychosis	3619	2.5
Pulmonary circulation disorder	2290	1.6
Renal failure	14713	10.2
Solid tumor	6518	4.5
Valvular disease	10172	7.1
Weight loss	4205	2.9
New injury scaling score	16399	11.3

The total in-hospital patient discharge charges had an average of $318,876.34/year with an average discharge cost of $31,887.63/patient; indicating the substantial inpatient burden of trauma among Paget's Disease patients in the United States. The minimum discharge charge per year was in 2001 with $26,682.5, while the maximum discharge charge was in 2009 with $36,207.66. Several comorbidities investigated were associated with significantly higher hospitalization charges ($p < 0.05$). For example, congestive heart failure (exp (b)=1.06), deficiencies anemia (exp (b)=1.16), chronic blood loss (exp (b)=1.20), coagulopathy (exp (b)=1.28), lymphoma (exp (b)=1.10), electrolytes disorders (exp (b)=1.13), metastatic cancer (exp (b)=1.16), obesity (exp (b)=1.07), paralysis (exp (b)=1.09), pulmonary circulation disorders (exp (b)=1.15) renal failure (exp (b)=1.05) and weight loss (exp (b)=1.39). Depression (exp (b)=0.92) and drug abuse (exp (b)=0.79) were associated with significantly lower charges.

Regarding hospital characteristics, higher cost was significantly with hospitals with both medium (exp (b)=1.22) and large bed size hospitals (exp (b)=1.44) relative to hospitals with small bed sizes. Also teaching (exp (b)=1.15), urban hospitals (exp (b)=1.59) compared rural, western hospitals (exp (b)=1.34) compared to other regions were significantly associated with increased hospital charges. On the other, total hospital charges were decreased in hospitals in the mid-western or southern region compared to hospitals in the northern or western regions.

Concerning patients characteristics, lower costs were associated with older patients (exp (b)=0.99), female patients (exp (b)=0.93), patients who paid with Medicaid (exp (b)=0.88) or other type of payment (exp (b)=0.87), as well as the no charge patients (exp (b)=0.73). On the other hand, patients with household income of 45,000 and over (exp (b)=1.08) were significantly associated with higher total hospital charges.



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Number of cases	16058	16585	15838	14395	14734	14609	13853	14106	12290	12401

Figure 1. The number of cases hospitalized with Paget's disease from 2001-2010

Table 4. Adjusted odds ratio for inpatient mortality among Paget's disease patients, stratified by trauma and non-trauma from 2001 to 2010

	Overall			Trauma			Non-Trauma		
DIED	Odds Ratio	P>|t|	95% Conf. Interval	Odds Ratio	P>|t|	95% Conf. Interval	Odds Ratio	P>|t|	95% Conf. Interval
Primary payer (Medicare reference)									
Medicaid	1.17	0.67	0.56-2.42	4.63	0.166	0.53-40.49	1.05	0.901	0.48-2.28
Private insurance	1.27	0.11	0.95-1.71	0.81	0.648	0.32-2.02	1.32	0.082	0.96-1.82
Self-pay	0.95	0.94	0.22-4.11	1			1.04	0.954	0.23-4.64
No charge	1			1			1		
Other	3.93	0.00	2.10-7.33	4.41	0.047	1.02-19.10	4.07	0.000	2.08-7.97
Hospital bed size (smallsize reference)									
Medium size	1.06	0.66	0.82-1.37	1.72	0.214	0.73-4.03	1.01	0.948	0.77-1.31
Large size	1.28	0.03	1.03-1.61	2.22	0.042	1.03-4.81	1.22	0.093	0.97-1.53
Rural hospital	0.75	0.01	0.67-0.94	0.91	0.813	0.43-1.94	0.74	0.014	0.59-0.94
Hospital region (north reference)									
Midwest	0.69	0.00	0.57-0.84	0.36	0.003	0.18-0.71	0.74	0.004	0.60-0.90
South	0.79	0.02	0.65-0.96	0.73	0.303	0.41-1.32	0.78	0.022	0.64-0.96
West	1.20	0.09	0.97-1.49	0.99	0.974	0.48-2.03	1.24	0.065	0.99-1.57
Teaching hospital	1.12	0.14	0.96-1.32	1.24	0.397	0.75-2.07	1.10	0.245	0.93-1.31
Year (2001 reference)									
2002	0.93	0.60	0.70-1.23	2.03	0.130	0.81-5.06	0.86	0.352	0.64-1.17
2003	0.94	0.69	0.70-1.27	1.67	0.305	0.63-4.44	0.89	0.476	0.64-1.23
2004	0.96	0.76	0.72-1.27	1.38	0.552	0.48-3.99	0.92	0.578	0.68-1.24
2005	0.72	0.03	0.53-0.97	0.81	0.730	0.25-2.62	0.71	0.033	0.52-0.97
2006	0.59	0.00	0.42-0.82	1.02	0.969	0.33-3.19	0.56	0.001	0.39-0.78
2007	0.65	0.01	0.47-0.91	1.02	0.971	0.36-2.91	0.62	0.009	0.44-0.89
2008	0.55	0.00	0.40-0.76	0.50	0.264	0.15-1.68	0.56	0.001	0.40-0.78
2009	0.58	0.003	0.40-0.83	0.90	0.852	0.30-2.72	0.54	0.002	0.37-0.79
2010	0.46	0.000	0.31-0.69	0.45	0.273	0.11-1.86	0.47	0.000	0.31-0.70
_IZIPINC_Q~2 |	0.99	0.948	0.78-1.26	1.41	0.394	0.64-3.10	0.95	0.720	0.74-1.23
_IZIPINC_Q~3 |	1.07	0.589	0.84-1.36	0.93	0.849	0.42-2.03	1.09	0.514	0.84-1.40
_IZIPINC_Q~4 |	0.98	0.853	0.77-1.24	0.91	0.804	0.44-1.87	0.99	0.966	0.77-1.28
Age	1.05	0.000	1.04-1.06	1.05	0.002	1.02-1.09	1.05	0.000	1.04-1.06
Female sex	0.90	0.195	0.77-1.05	0.65	0.103	0.38-1.09	0.94	0.458	0.79-1.11
AHRQ morbidities									
AIDS	1			1			1		
ALCOHOL	1.35	0.442	0.63-2.88	1			1.70	0.161	0.81-3.59
Deficiency anemias	0.91	0.301	0.76-1.09	0.97	0.914	0.58-1.63	0.88	0.171	0.73-1.06
Rheumatoid arthritis	1.23	0.331	0.81-1.85	0.35	0.339	0.04-3.02	1.31	0.205	0.86-2.00
Chronic blood loss	0.93	0.764	0.56-1.52	1.30	0.746	0.26-6.49	0.89	0.667	0.53-1.50
Congestive heart failure	2.00	0.000	1.66-2.40	2.20	0.003	1.31-3.69	1.94	0.000	1.60-2.36
Chronic pulmonary disease	1.16	0.091	0.98-1.38	1.15	0.619	0.67-1.97	1.16	0.118	0.96-1.40
Coagulopathy	1.60	0.005	1.15-2.24	1.90	0.173	0.75-4.78	1.56	0.019	1.08-2.27
Depression	0.95	0.691	0.73-1.23	0.98	0.958	0.44-2.17	0.94	0.660	0.71-1.24
Diabetes	1.00	0.972	0.81-1.22	0.77	0.427	0.41-1.47	1.01	0.921	0.81-1.26
Diabetes with chronic complications	1.00	0.995	0.66-1.50	0.39	0.179	0.10-1.53	1.06	0.783	0.69-1.63

Drug abuse	1			1			1		
Hypertension	0.66	0.000	0.57-0.76	0.50	0.003	0.32-0.79	0.67	0.000	0.58-0.78
Hypothyroidism	0.79	0.048	0.63-1.00	0.74	0.378	0.38-1.44	0.79	0.059	0.62-1.01
Liver disorder	1.26	0.488	0.65-2.46	2.36	0.484	0.21-26.09	1.25	0.532	0.62-2.49
Lymphoma	1.41	0.259	0.78-2.54	1.38	0.763	0.17-11.35	1.41	0.277	0.76-2.61
Electrolyte disorder	2.22	0.000	1.88-2.63	2.72	0.000	1.63-4.52	2.17	0.000	1.82-2.59
Metastatic cancer	2.19	0.000	1.51-3.18	2.17	0.300	0.50-9.42	2.19	0.000	1.49-3.22
Neuropathy	1.62	0.000	1.32-1.98	0.64	0.279	0.28-1.44	1.81	0.000	1.46-2.25
Obesity	0.41	0.023	0.19-0.89	0.88	0.912	0.09-8.76	0.38	0.019	0.17-0.85
Paralysis	2.02	0.000	1.41-2.90	5.19	0.002	1.80-14.93	1.80	0.003	1.22-2.66
Peripheral vascular disorders	0.96	0.796	0.74-1.26	1.19	0.692	0.49-2.89	0.93	0.646	0.70-1.25
Psychoses	0.93	0.783	0.57-1.53	0.36	0.343	0.04-2.97	1.01	0.949	0.61-1.68
Pulmonary circulation disorders	1.03	0.909	0.63-1.68	0.52	0.480	0.08-3.19	1.14	0.608	0.69-1.88
Renal failure	2.00	0.000	1.63-2.43	3.90	0.000	2.19-6.92	1.83	0.000	1.47-2.28
Tumor	1.02	0.924	0.72-1.44	1.81	0.261	0.64-5.07	0.96	0.850	0.66-1.40
Peptic ulcer disease	0.65	0.546	0.16-2.66	1			0.69	0.611	0.17-2.82
Valvular disease	1.05	0.687	0.82-1.35	1.15	0.699	0.55-2.43	1.04	0.769	0.80-1.35
Weight loss	1.98	0.000	1.47-2.69	2.22	0.090	0.88-5.59	2.00	0.000	1.46-2.73
niss	1.00	0.750	0.98-1.03	1.02	0.006	1.01-1.04	1		
_cons	0.00	0.000	0.00-0.00	0.00	0.000	$6.7e^{-06}$-.00	0.00	0.000	0.00-0.00
*Adjusted for age, gender, median income, the expected primary payer, the hospital location, region, bed size, teaching status, years from 2001-2010, AHRQ comorbidities and NISS									

4. Discussions

Using a nationally representative sample of clinical and economical characteristics, this investigation estimated the inpatient burden of Paget's Disease in the United States from 2001 to 2010. In this time period, 144,869 hospitalizations occurred and the inpatient, mortality rate was 2.9%. Trauma was associated with 76.95% of the hospitalizations and the total in-hospital patient discharge costs had an average of $318,876.34/year with an average discharge cost of $31,887.63/patient; indicating the substantial inpatient burden of trauma among Paget's Disease patients in the United States. Moreover, given the recognition of Paget's Disease as a disease with systemic manifestations and the increased occurrence of certain comorbid conditions in Paget's Disease patients (1,3), the current study quantified the independent associations between a number of these comorbid conditions and the clinical and economic outcomes of mortality and costs in the inpatient settings. After adjusting for patient characteristics (age, gender, primary payer, median household income), hospital characteristics (hospital region, location, teaching status and bed size), and year (2001 to 2010), several comorbidities were significantly associated with both higher mortality as well as higher cost including congestive heart failure, electrolyte disorders, metastatic tumors, obesity, paralysis, renal failure and weight loss.

This investigation provided a more recent nationally representative and generalizable estimate of the inpatient burden of Paget's Disease in the United States. Previous studies used data sources which are now more than a decade old ((1,3)). The inclusion criteria enabled the investigation to capture the largest proportion of Paget's Disease patients hospitalized from 2001 to 2010. Furthermore, this current study was able to consider the independent associations between these outcomes and a number of important comorbid conditions while adjusting for several possible confounders in the inpatient setting. There have been no articles describing total hospital charges for Paget's Disease patients. The findings add to the understanding of comorbidities and Paget's Disease by identifying co-existing diseases that pose a greater disease burden specifically in hospitalized patients.

There was a significant decrease on the number of hospitalized cases as well as the mortality associated with Paget's Disease from 2001 to 2010. Similar reductions in the prevalence of Paget's Disease has been noted over the recent years in several surveys from Five different studies among Europe and New Zealand [1,15,19,12,20].

Although most comorbid conditions were associated with increased mortality, these differences may not be clinically relevant despite their statistical significance. Nevertheless, consistent with the general trend in the results of our investigations, several

studies have previously reported associations between individual comorbidities and increased mortalities among Paget's Disease patients, even when controlling for several other potential confounding variables. Two reasons have been suggested for the increased mortality associated with certain comorbid conditions, specifically trauma and paralysis: 1) the pathology of Paget's disease; and 2) as a direct consequence of the disease which can lead systemic manifestations and development of other comorbid conditions.

Stratification by trauma showed some changes in the magnitude of the odds ratios associated with some of the comorbid conditions. For example, the adjusted odds ratio for inpatient mortality for renal failure among Paget's Disease patients who were admitted with a trauma event 3.89 compared to 1.98 for all cases. Moreover, the adjusted odds ratio for mortality associated with comorbid condition for paralysis was 5.19 for trauma patients compared to 2.02 for all cases. These findings suggest that the worse outcomes among Paget's Disease patients were observed for trauma cases and observed association may differ for certain comorbid conditions dependent on the study settings and follow up. Many studies have previously assessed the role of comorbid conditions in predicating mortality among Paget's Disease patients [1,3,6].

The increases in costs associated with specific comorbid conditions ranged from a factor of 1.28 for coagulopathy to 0.79 for drug abuse. Depression and drug abuse were associated with significantly lower costs. In terms of hospital characteristics, hospitals with medium and large bed size compared to small bed size, teaching as well as urban hospitals compared to rural hospitals were significantly associated with higher costs as well as higher mortality. Overall the association between costs and hospital characteristics has known to exist 18. Larger hospitals may more likely be located in urban areas which make treatment in these hospitals more expensive due to reasons for example bigger size, increased labor cost as well as more sophisticated services [18].

Teaching hospitals are associated with higher cost due to several reasons including their role in medical education, more complex range of services, treatment of severe cases as well as having more sophisticated equipment [18].

The strengths of the study come from its sample size; analyzing large sample size increase the power of the analysis and decrease the error margin. Moreover, this study is innovative because there are no current studies describing the trend of Paget's Disease in the U.S. Also, there are no current data about morbidity and mortality associated with Paget's Disease in the U.S. or the discharge cost for the hospitalized patients.

There were several potential limitations to consider in this study. This study is a retrospective database analyses with associated coding errors, omissions and unmeasured confounding factors. Moreover, this study lacked data from individuals living with Paget's Disease outside the hospital system or from all hospitals in the US. Also, the large sample size of this study can affect the multivariate estimate by making them reach the statistical significance without reaching the clinical relevance. The study concluded that the number of cases and mortalities among Paget's Disease hospitalized patients has decreased form 2001-2010. Also, we concluded that the increased mortality and total hospital charges were associated with co-presence of specific severe morbidities and with trauma. Finally, we can say that increased understanding of these morbidities remains essential to improve treatment and patient outcomes.

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References

1. Cyrus Cooper, N. C. (2006). Update on the Epidemiology of Paget's Disease of Bone. *journal of bone and mineral research*, P3-8.
2. M J HADDAWAY, M. W. (2007). Effect of age and gender on the number and distribution of sites. *The British Journal of Radiology*, 532–536.
3. Reddy, S. V. (2006). Etiologic factors in Pa get's disease of bone. *Cellular and Molecular Life Sciences*, 391-398.
4. Kumar A Vinod, D. M. (2006). Paget's disease of bone. *ORTHOPAEDIC II: SOFT TISSUE, METABOLISM AND MALIGNANCY*, 390-391.
5. C. COOPER, E. D. (1999). Epidemiology of Paget's Disease of Bone. *Bone*, 3S-5S.
6. Barker, D. J. P. (1984) The epidemiology of Paget's disease. Br Med Bull 40:396–400.
7. Ralston, S. H. (2008). Pathogenesis of Paget's disease of bone. Bone, 819-825.
8. Barker, D. J. P., Chamberlain, A. T., Guyer, P. B., and Gardner, M. J. (1980) Paget's disease of bone; the Lancashire focus. Br Med J 280:1105–1107.

9. Rainier Luz Reis, M. F. (2012). Epidemiology of Paget's disease of bone in the city of Recife, Brazil. Rheumatol International, 3087-3091.
10. Ana O. Hoff, B. T. (2011). Epidemiology and risk factors for osteonecrosis of the jaw in cancer patients. ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 47-54.
11. Jonathan M. Rasmussen, M. L. (2008). Placement and Restoration of Dental Implants in a Patient with Paget's Disease in Remission: Literature Review and Clinical Report. Journal of Prosthodontics, 35-40.
12. Sonja Bastin, H. B. (2009). Paget's disease of bone—becoming a rarity? Rheumatology, 1232-1235.
13. Alain Sarauxa, Catherine Brun-Strangb, Viviane Mimaudc, Anne-Marie Vigneronb, Antoine Lafumac (2007). Epidemiology, impact, management, and cost of Paget's disease of bone in France. Joint Bone Spine,74:90-95.
14. Tim Cundy, I. R. (2012). Paget's disease of bone. Clinical Biochemistry, 43-48.
15. R. D. TIEGS, C. M. (2000). Long-Term Trends in the Incidence of Paget's Disease of bone. Bone, 423-427.
16. Daniela Merlotti, L. G. (2005). Characteristics and Familial Aggregation of Paget's Disease of Bone in Itlay. OURNAL OF BONE AND MINERAL RESEARCH, 1356-1364.
17. Siris, E. S. (1994). Epidemiological Aspects of Paget's Disease: Family History and Relationship to Other Medical Conditions. Seminars in Arthritis and Rheumatism, 222-225.
18. Utah Health Data Committee. (1993). Hospital Financial and Utilization Profile Standard Report No.: ST-1 [Internet]. Utah Office of Health Data Analysis, Utah Department of Health.; c1995.
19. Gennari L, Di Stefano M, Merlotti D, Giordano N, Martini G, Tamone C. (2005) Prevalence of Paget's disease of bone in Italy. J Bone Miner Res;20:1845–50.
20. Doyle T, Gunn J, Anderson G, Gill M, Cundy T. (2002). Paget's disease in New Zealand: evidence for declining prevalence. Bone;31:616–9.
21. HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2000-2010. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/nisoverview.jsp.
22. Osler T, Baker S, Long W. (1997). A modification of the injury severity score that both improves accuracy and simplifies scoring. J Trauma;41:922–6.
23. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8-27.
24. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43(11):1130-1139.

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