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Comparative Effectiveness of Ceftriaxone in Combination with a Macrolide Compared with Ceftriaxone Alone for Pediatric Patients Hospitalized with Community Acquired Pneumonia

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Abstract

Background—Guidelines for management of community acquired pneumonia recommend empiric therapy with a macrolide and beta-lactam when infection with *Mycoplasma pneumoniae* is a significant consideration. Evidence to support this recommendation is limited. We sought to determine the effectiveness of ceftriaxone alone compared to ceftriaxone combined with a macrolide with respect to length-of-stay and total hospital costs.

Methods—We conducted a retrospective cohort study of children 1–17 years with pneumonia, using Poisson regression and propensity-score analyses to assess associations between antibiotic and length of stay. Multivariable linear regression and propensity-score analyses were used to assess log-treatment costs, adjusting for patient and hospital characteristics and initial tests and therapies.

Results—4701 children received combination therapy and 8892 received ceftriaxone alone. Among children 1–4 years of age, adjusted models revealed no significant difference in length of stay, with significantly higher costs in the combination therapy group(cost ratio 1.08 (95% CI 1.05 – 1.11)). Among children 5–17 years of age, children receiving combination therapy had a shorter length of stay(RR 0.95 (95% CI, 0.92– 0.98)), with no significant difference in costs(cost ratio 1.01 (95% CI, 0.98 –1.04)).

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Conclusions—Combination therapy did not appear to benefit preschool children but was associated with higher costs. Among school-aged children, combination therapy was associated with a shorter length of stay without a significant impact on cost. Development of sensitive point-of-care diagnostic tests to identify children with *M. pneumoniae* infection may allow for more focused prescription of macrolides and enable comparative effectiveness studies of targeted provision of combination therapy.

Keywords

community acquired pneumonia; comparative effectiveness; child; adolescent; antibiotics

Introduction

Community acquired pneumonia (CAP) is a common illness in the pediatric population with an annual incidence of 34–40 cases per 1000 in children younger than 5 years of age and 7 cases per 1000 in adolescents in Europe and North America.[1,2] It is the leading cause of pediatric hospitalization in the United States, with more than 160,000 hospital admissions annually.[3] Approximately three quarters of these hospitalizations occur at general community hospitals, while the remainder occur at children's hospitals.[4]

Despite significant disease burden and healthcare costs, little research has been carried out to determine the effectiveness of antibiotic regimens for CAP among hospitalized children, particularly in general community hospitals where the majority of children receive their care. Ceftriaxone, the most common first-line antibiotic for inpatient management, provides broad antimicrobial coverage but does not treat *Mycoplasma pneumonaie*, an atypical organism believed to play a causative role in CAP in up to one third of children.[5–8] While traditionally thought to predominantly affect school-aged children, recent studies suggest that this organism also plays a significant role in children less than five years of age.[5,7–9] However, true rates of *M. pneumonaie* infection are difficult to ascertain given difficulties interpreting serology and limited rapid diagnostic testing availability in many settings.

Current national treatment guidelines advise empiric therapy with a macrolide in addition to a beta-lactam for hospitalized children for whom infection with *M. pneumoniae* is a significant concern.[10] However, in summarizing the research influencing this recommendation, the authors acknowledge a paucity of evidence. A recent systematic review concluded that there is insufficient evidence that antibiotics are effective in children with CAP caused by *M. pneumoniae*,[9] further highlighting the uncertainty about whether addition of a macrolide provides a treatment advantage over beta-lactam antibiotics alone.

The objective of this study was to determine the comparative effectiveness of ceftriaxone alone relative to ceftriaxone in combination with a macrolide for the treatment of CAP in both preschool and school-aged hospitalized children with respect to length of hospital stay (LOS) and total hospital costs.

Materials and Methods

Study Design & Eligibility Criteria

We conducted a retrospective cohort study of children and adolescents (hereafter referred to as children) one to 17 years of age admitted between July 1, 2007 and June 30, 2010 to hospitals that contribute data to the Perspective Data Warehouse (PDW) (Premier Healthcare Informatics, Charlotte, NC), a highly detailed administrative database that measures healthcare utilization. PDW includes geographically diverse hospitals that closely represent the composition of acute care hospitals nationwide, incorporating approximately 15% of all hospitalizations in the United States. PDW has been previously described[11–13] and has been used in several studies of pediatric populations.[14–16] The database contains fully de-identified information including demographic characteristics, length of stay, all International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM) discharge diagnoses, as well as a date-specific record of all billed items, including diagnostic tests, medications and their associated costs. It does not contain clinical data such as physical exam findings or laboratory test results.

We included children with a principal diagnosis (ICD-9-CM) of pneumonia (480–483 or 485–487.0), applying a previously validated algorithm.[17] All patients received either ceftriaxone alone, or ceftriaxone and a macrolide (oral or parenteral azithromycin, erythromycin or clarithromycin) beginning in the emergency department or on the first day of hospitalization. Because we were interested in characterizing the role of macrolides among previously well children, the target population of the national clinical practice guidelines, we excluded infants less than one year of age, those with a concurrent diagnosis of bronchiolitis, and children with complex chronic conditions using an established classification scheme.[18] Patients transferred to or from other acute care facilities or who left hospital against medical advice were excluded as we were unable to accurately assess LOS or full course of hospital treatments.

Treatment and Outcome Variables

Our primary independent variable was antibiotic treatment initiated in the emergency department or on the first day of hospitalization: parenteral ceftriaxone alone or in combination with a macrolide (hereafter referred to as combination therapy). The primary outcome measures were LOS, reported in days, and total costs of hospitalization, reported in United States dollars (USD). For approximately 75% of hospitals contributing data to PDW, these reflected actual hospital costs taken from internal cost accounting systems, whereas the remaining hospitals provided cost estimates based on Medicare cost-to-charge ratios. Secondary outcomes included: (i) transfer to the intensive care unit on or after the second day of hospitalization, a measure of clinical deterioration; (ii) inpatient mortality; and (iii) readmission to hospital within 30 days of hospital discharge, including all-cause readmissions and pneumonia-related readmissions.

Patient, hospital, and pneumonia management variables

Study participants were characterized on the basis of age, gender, race/ethnicity (as recorded by the staff of participating hospitals using hospital-defined options), insurance status, and

comorbid conditions including asthma, influenza, and disorders of fluids and electrolytes. Asthma was defined as (i) an ICD-9-CM code for asthma (493.0–493.9), or (ii) provision of long term asthma control medications (long-acting beta agonists, inhaled corticosteroids, leukotriene antagonists or mast cell stabilizers) on the first day of hospitalization, presumed to represent continuation of home therapies. Influenza was defined as an ICD-9-CM code of 487 or 488 (influenza due to identified avian influenza virus). Characteristics of the admitting hospitals included geographic region, bed size, urban/rural location, children's hospital versus general community hospital, and teaching status. Children's hospitals included both freestanding children's hospitals and children's hospitals within larger adult centers, defined as institutions that had at least ten pediatric subspecialties recorded in the database. Respiratory season was defined as October to March.

We examined detailed billing and ICD-9-CM procedure codes to identify the use of diagnostic tests and adjunctive therapies for patients with pneumonia, outlined in Table 1. Initial investigations and adjunctive therapies were defined as those provided on the first day of hospitalization.

Statistical analysis

We calculated patient-level summary statistics using frequencies and percents for categorical variables and medians and interquartile ranges for continuous variables. Unadjusted associations between antibiotic treatment group and patient and hospital characteristics, initial therapies, and outcomes were assessed using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. To assess for potential differential effects of combination therapy among children with asthma relative to those without, we assessed for an interaction between antibiotic regimen and asthma.

Poisson regression was used to assess associations between antibiotic regimen and LOS, adjusting for patient and hospital characteristics and initial investigations and therapies. Multivariable linear regression models were used to assess the log-transformed total hospital costs associated with each antibiotic regimen, again adjusting for patient and hospital characteristics and initial investigations and therapies. All models were adjusted for the effects of within-hospital correlation using generalized estimating equations. Costs were trimmed at 3 standard deviations above the mean and log-transformed due to extreme positive skew. Our initial models were adjusted for age group but, due to age-treatment interactions, we evaluated and report age stratified models. Variables entered into the multivariable models, determined *a priori*, included all patient and hospital characteristics shown in Table 1, and initial investigations and adjunctive therapies with p-values ≤ 0.1 observed in our initial bivariate analyses.

To address the potential issue of confounding by indication (that patients with more severe disease presentation were more likely to receive combination therapy), a propensity score model to predict initial antibiotic therapy was constructed for each age group, incorporating all patient and hospital characteristics, comorbid conditions, and initial investigations and adjunctive therapies listed in Table 1. We applied the propensity score in two ways: (i) as a covariate in the multivariable models, and (ii) in a propensity-matched subset, using a greedy algorithm to match 1:1 patients who received ceftriaxone alone with those who

received combination therapy, adjusting for unbalanced co-variates. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Hypothesis testing was two sided with a type I error rate of α=0.05. Because the data do not contain identifiable information, the Institutional Review Board at Baystate Medical Center determined that this study did not constitute human subjects research.

Results

A total of 32,845 children aged 1–17 years of age were admitted to 294 hospitals during the study period. As illustrated in Supplemental Digital Content 1 (figure), 13,593 children at 268 hospitals met our eligibility criteria. Children excluded from the study included 46 that received ampicillin alone, 1 that received ampicillin-macrolide combination therapy, 818 that received a second generation parenteral cephalosporin, and 5 that received a second generation parenteral cephalosporin in combination with a macrolide. Approximately one third of children (n=4701) received ceftriaxone-macrolide combination therapy, while two-thirds (n=8892) received ceftriaxone alone. Approximately one quarter of preschool children ages 1–4 years were treated with combination therapy in comparison to half of school aged children (5–17 years).

As shown in Table 1, children receiving combination therapy were, on average, older, more likely to have private insurance, and were less frequently admitted during respiratory season than those receiving ceftriaxone alone. More than 40% of all children in our sample had asthma concurrent with pneumonia (n=5873). Children receiving combination therapy were less frequently admitted to teaching hospitals. There were also small but statistically significant differences between the groups in terms of geographic region, hospital size, and hospital type. Children who received combination therapy were more likely to have received adjunctive therapies in the emergency department or on the first day of hospitalization (Table 1). Approximately one-third received oral or intravenous steroids, including 40.3% (n=1892) of children in the combination therapy group and 29.4% (n=2610) in the ceftriaxone group. More than half of children in both groups received beta-agonists, including almost two-thirds of children in the combination therapy group.

In our unadjusted analysis, LOS was not significantly different between the groups; both had a mean length of stay of 2.4 days and a median of 2 days (IQR 1–3 days). However, unadjusted total hospital costs were significantly higher in the combination therapy group; mean total cost was 4317 USD (median 3362 USD, IQR 2304–5099) in the combination therapy group and 3831 USD in the ceftriaxone alone group (median 3023 USD, IQR 2083–4512). When stratified by age group, there was no significant difference in the LOS among preschool-aged children in the two treatment groups but total hospital costs were approximately 20% higher among children who received combination therapy (Table 2). Among school-aged children, the combination therapy group had a LOS approximately 5% shorter than that observed in the ceftriaxone alone group with significantly higher total hospital costs. There were no significant differences between the treatment groups in our secondary outcomes, including transfer to the intensive care unit, inpatient mortality, or readmission.

The interaction between antibiotic regimen and age group was statistically significant ($p < 0.001$), so all multivariable analyses are age-stratified. The interaction between antibiotic regimen and asthma was non-significant ($p > 0.23$ for both preschool and school-aged children for LOS and cost) and therefore excluded from further analyses. Among preschool-aged children, there were no significant differences in the adjusted LOS between the treatment groups (Table 3). Both covariate adjusted and propensity score adjusted models resulted in similar relative risk estimates. Total hospital costs were significantly higher among preschool-aged children who received combination therapy.

Among school-aged children, the significantly decreased LOS observed in our unadjusted analysis remained when we adjusted for patient and hospital characteristics (Table 3). In covariate-adjusted models, the average length of stay for patients who received combination therapy was 5% less than those who received ceftriaxone alone (RR 0.95; 95% CI, 0.92–0.98). This result persisted and was almost identical in our propensity matched analysis. In models of total hospital costs, no significant differences were observed in this age group.

Discussion

National clinical practice guidelines for pneumonia management among hospitalized children recommend empiric combination therapy with a macrolide and beta-lactam antibiotic for patients in whom infection with *M. pneumoniae* is a significant consideration.[10] Although commonly prescribed, our study suggests that combination therapy does not have a treatment advantage among preschool children with respect to LOS, transfer to the intensive care unit, or rate of hospital readmission. However, in this age group, combination therapy was associated with a significantly increased cost, reflecting increased resource utilization in this group. Among children and adolescents 5–17 years of age, combination therapy was associated with a shorter LOS with no significant difference in total hospital costs or rates of ICU transfer, mortality or readmission.

Ambroggio et al. explored the comparative effectiveness of empiric beta-lactam therapy and beta-lactam-macrolide combination therapy for pneumonia among patients admitted to freestanding children's hospitals and found that combination therapy was associated with a shorter LOS among school-aged children with no benefit to preschool children.[19] Our study confirms and extends their study findings to a larger sample inclusive of both children's hospitals and general community hospitals, where almost three quarters of children admitted to hospitals in the United States for pneumonia receive their care.[4] Taken together in the context of previous research, these studies call into question the utility of empiric combination therapy among preschool aged children, perhaps reflecting a lower rate of infection with *M. pneumonaie* or spontaneous clinical resolution of infection hypothesized to occur in this age group.[10,20,21] The magnitude of difference in LOS observed among school aged in our combination therapy cohort is considerably less than that observed by Ambroggio et al., which may reflect differences in the characteristics of patients admitted to general community hospitals, differences in availability of diagnostic testing, or differences in perceived risk of *M. pneumoniae* infection. Our adjusted odds ratio for length of stay translates into a need to treat seven school-aged children with combination therapy to result in one child staying in hospital for one less day. Given that approximately 56,000 school-

aged children were admitted to hospital with pneumonia in the United States in 2009,[4] on a national level this is equivalent to 8000 children and adolescents discharged from hospital one day sooner, which has clear implications for hospital resource utilization as well as quality of life for children and their families. However, this must be balanced against potential adverse effects associated with broad provision of macrolides, both from the perspective of individual patients' potential adverse effects, as well as the development of antibiotic resistance.[22,23] A recent Cochrane review concluded that *M. pneumonaie* cannot be reliably diagnosed on the basis of symptoms and signs,[24] while the utility of diagnostic testing is limited given difficulties interpreting serological results, lag time to culture results, and limited availability of rapid diagnostic technologies in many centers, particularly community hospitals. Macrolide prescribing, as well as macrolide resistance, has increased substantially in the last decade.[25] Development of rapid, sensitive point-of-care diagnostic tests or clinical prediction rules to identify children at highest risk of *M. pneumoniae* infection may allow for more focused prescription of macrolides while creating opportunities for comparative effectiveness studies of targeted provision of combination therapy.

Approximately forty percent of children in our cohort were admitted with concurrent diagnoses of pneumonia and asthma, highlighting the importance of future studies of pneumonia management among children with asthma. Frequent co-occurrence of asthma and pneumonia among hospitalized children has been previously reported in an analysis of the National Hospital Discharge Survey (NHDS), which noted that 24% of hospitalized children had concurrent pneumonia and asthma.[26] The higher rate of asthma seen in our cohort may reflect that, unlike the NHDS analysis, our asthma definition included an ICD-9-CM code for asthma in any secondary discharge diagnosis field and we excluded infants less than one year of age. The high rates of beta-agonist and steroid use on the first day of hospitalization further suggest that a large fraction of children presented to hospital with wheezing or signs of airway inflammation. Macrolides have both antimicrobial and anti-inflammatory properties,[27–29] and their use for chronic asthma management has been the subject of several studies and a Cochrane systematic review.[30–33] Despite the biologic plausibility that addition of a macrolide to ceftriaxone could reduce airway inflammation and result in decreased LOS among children with concurrent diagnoses of asthma and pneumonia, we did not find a significant interaction between asthma and macrolide use. However, forty percent of children in our cohort received oral or intravenous steroids in addition to a macrolide, which may have attenuated the anti-inflammatory effects of macrolides.

Our results should be interpreted in light of a number of limitations. First, we used ICD-9-CM codes to retrospectively identify patients with pneumonia, which may have resulted in potential misclassification. We attempted to minimize misclassification by using a previously validated ICD-9-CM algorithm[17] and by limiting our analysis to children who received our antibiotics of interest on the first day of hospitalization. However, this approach may have resulted in exclusion of some pneumonia cases. Second, because our analysis used administrative data, there may be additional factors associated with providers' decisions to provide combination therapy, such as clinical history or chest x-ray findings, which were

unavailable. Related to this, the outcomes available in PDW, such as length of stay and readmission rates, may be insensitive to differences in patients' functional status and quality of life, both of which would be beneficial to assess in determining the comparative effectiveness of antibiotics for pneumonia. By applying propensity-score matched analyses, we used a rigorous methodology to account for potential confounding by indication. However, there may be unmeasured confounders that influenced our observed outcomes. Third, we were very interested in understanding the potential interaction between asthma and antibiotic treatment and incorporated use of long term asthma control medications to supplement ICD-9-CM codes to identify cases. If these medications were used inappropriately, our definition may have overestimated the prevalence of asthma in our cohort. However, a similar proportion, 39.6% of children in our cohort, had an asthma diagnosis based on ICD-9-CM codes alone. Further study is needed to explore optimal management of patients presenting with concurrent asthma and pneumonia. Lastly, given very low rates of use of ampicillin use in our cohort, we limited our comparison to ceftriaxone with or without a macrolide, despite national recommendations that ampicillin be used as the first-line antibiotic for CAP treatment.[10]

This study applied a retrospective observational study design to determine the comparative effectiveness ceftriaxone-macrolide combination therapy for pneumonia management in routine clinical practice. We found that combination therapy did not appear to benefit preschool children but was associated with higher costs, while among school-aged children, combination therapy was associated with a shorter length of stay without a significant impact on cost. Clinical trials assessing the efficacy of combination therapy for pediatric pneumonia caused by *M. pneumonaie* have not been conducted previously and are needed to ascertain the magnitude of benefit of adding a macrolide among school-aged children. Decision analysis models determining the costs and benefits of early initiation of a macrolide compared with delayed addition until the second or third day of hospitalization could also inform clinical guidelines while minimizing adverse effects of non-judicious macrolide use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient and hospital characteristics and initial management among children with pneumonia treated with ceftriaxone alone relative to those treated with ceftriaxone in combination with a macrolide.

	Ceftriaxone alone (n=8892)		Ceftriaxone + macrolide (n=4701)		p-value
Patient Characteristics	**N**	**%**	**N**	**%**	
Gender (% male)	4814	54.1	2574	54.8	0.49
Age, yrs (median,IQR)	3 (1–5)		5 (2–8)		<0.001
1–4 yrs	6308	70.9	2282	48.5	<0.001
5–17 yrs	2584	29.1	2419	51.5	
Race/ethnicity					
White	4414	49.6	2325	49.5	<0.001
Black	1644	18.5	751	16.0	
Hispanic	1178	13.2	723	15.4	
Other	1656	18.6	902	19.2	
Insurance status					
Public payer	4605	51.8	2238	47.6	<0.001
Private payer	3839	43.2	2210	47.0	
Uninsured	327	3.7	191	4.1	
Unknown	121	1.4	62	1.3	
Admission during respiratory season	5877	66.09	2972	63.22	<0.001
Comorbid conditions					
Asthma	3605	40.5	2268	48.2	<0.001
Influenza	474	5.3	220	4.7	0.10
Fluid and electrolyte disorders	2649	29.8	1149	24.4	<0.001
Hospital Characteristics					
Urban (vs rural)	6993	78.6	3711	78.9	0.69
Teaching status (vs non-teaching)	3289	37.0	1517	32.3	<0.001
Bedsize					
<=200 beds	1656	18.6	1001	21.3	<0.001
201–400 beds	3781	42.5	1708	36.3	
400+ beds	3455	38.9	1992	42.4	
Region					
Northeast	1206	13.6	538	11.4	<0.001
Midwest	1703	19.2	888	18.9	
West	1092	12.3	754	16.0	

Patient Characteristics	Ceftriaxone alone (n=8892) N	%	Ceftriaxone + macrolide (n=4701) N	%	p-value
South	4891	55.0	2521	53.6	
Children's hospital (vs general community hospital)	1996	22.4	1135	24.1	0.03
Initial Investigations					
Blood culture	6881	77.4	3629	77.2	0.80
Chest x-ray	7363	82.8	3928	83.6	0.27
Chest ultrasound	13	0.1	7	0.1	0.97
Chest CT	48	0.5	46	1.0	<0.001
Arterial blood gas	226	2.5	166	3.5	0.001
Acute phase reactants (ESR or CRP)	1493	16.8	872	18.5	0.01
Urine culture	1404	15.8	570	12.1	<0.001
Lumbar puncture	43	0.5	5	0.1	<0.001
Test for viral pathogens	3177	35.7	1706	36.3	0.52
Initial Adjunctive Therapies					
IV or oral steroids	2610	29.4	1892	40.3	<0.001
Short-acting beta-agonists	4966	55.9	3047	64.8	<0.001
Intravenous fluids	5533	62.2	3225	68.6	<0.001
Chronic asthma medications	1184	13.3	960	20.4	<0.001
Intensive care unit admission	245	2.8	199	4.2	<0.001
Non-invasive ventilation	46	0.52	23	0.49	0.83
Intubation and ventilation	11	0.12	6	0.13	0.95

Table 2

Primary and secondary outcomes among patients receiving pneumonia treatment with ceftriaxone alone compared to cefriaxone with addition of a macrolide, stratified by age group.

Outcome	Ceftriaxone alone (n=8892)	Ceftriaxone + macrolide (n=4701)	p-value
Ages 1–4 years			
Length of stay, days (mean, SD) Median (IQR)	2.37 (1.51) 2 (1–3)	2.43 (1.61) 2 (1–3)	0.19
Total hospital costs, USD (mean, SD) Median (IQR)	$3691 (3354) $2949 (2051–4355)	$4328 (3689) $3356 (2263–5210)	<0.0001
Transfer to intensive care unit >= day 2 (n, %)	35 (0.8%)	7 (0.4%)	0.14
Inpatient mortality (n, %)	1 (0.01%)	0 (0%)	0.57
All cause < 30 d readmission (n, %)	58 (0.9%)	24 (1.1%)	0.58
Pneumonia-related <30 d readmission (n, %)	41 (0.7%)	19 (0.8%)	0.37
Ages 5–17 years			
Length of stay, days (mean, SD) Median (IQR)	2.60 (1.72) 2 (2–3)	2.48 (1.56) 2 (1–3)	0.02
Total hospital costs, USD (mean, SD) Median (IQR)	$4173 (3874) 3258 (2191–4896)	$4306 (5330) 3366 (2328–4979)	0.03
Transfer to intensive care unit >= day 2 (n, %)	26 (1.3%)	13 (0.7%)	0.71
Inpatient mortality (n, %)	0 (0%)	1 (0.04%)	0.30
All cause < 30 d readmission (n, %)	28 (1.1%)	16 (.7%)	0.10
Pneumonia-related <30 d readmission (n, %)	12 (0.5%)	11 (0.6%)	0.96

Table 3

Adjusted and unadjusted models for length of stay and total hospital costs among children treated with ceftriaxone in addition to a macrolide relative to ceftriaxone alone.

	Length of stay		Total hospital cost	
Ages 1–4 years	**Relative Risk (95% CI)**	**p-value**	**Cost Ratio (95% CI)**	**p-value**
Unadjusted	1.00 (0.97, 1.03)	0.88	1.08 (1.05, 1.11)	<0.0001
Covariate adjusted	0.98 (0.95, 1.01)	0.31	1.04 (1.01,1.07)	<0.01
Propensity score & covariate adjusted	0.99 (0.96, 1.02)	0.38	1.04 (1.01,1.07)	<0.01
Propensity score matched*	1.02 (0.99, 1.05)	0.32	1.07 (1.03, 1.10)	<.0001
Ages 5–17				
Unadjusted	0.96 (0.93, 0.99)	0.01	1.03 (0.99, 1.06)	0.12
Covariate adjusted	0.95 (0.92,0.98)	<0.01	1.01 (0.98, 1.04)	0.60
Propensity score & covariate adjusted	0.95 (0.92, 0.98)	<0.01	1.01 (0.98, 1.04)	0.55
Propensity score matched*	0.96 (0.93, 0.99)	<0.01	1.01 (0.98,1.04)	0.62

* adjusted for unbalanced covariates