Application of Propensity Score Methods in Comparative Effectiveness Research

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Outline

- Propensity Score Methodology
- Background
- Research Question
- Methods
- Results
- Conclusions
- Wrap Up

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Potential in CER:

- Rare outcomes and numerous variables to take into consideration
- Effectiveness of a drug may vary according to the strength of the indication for its use
- Confounding by Indication

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Propensity Score

- The probability of a patient receiving a specific treatment conditional on observed covariates.

- $\text{Trt (0/1)} = B_0 + B_1 * X_1 + \ldots + B_n * X_n + B_{n+1} * X_1 * X_2$

- Covariate selection methods vary

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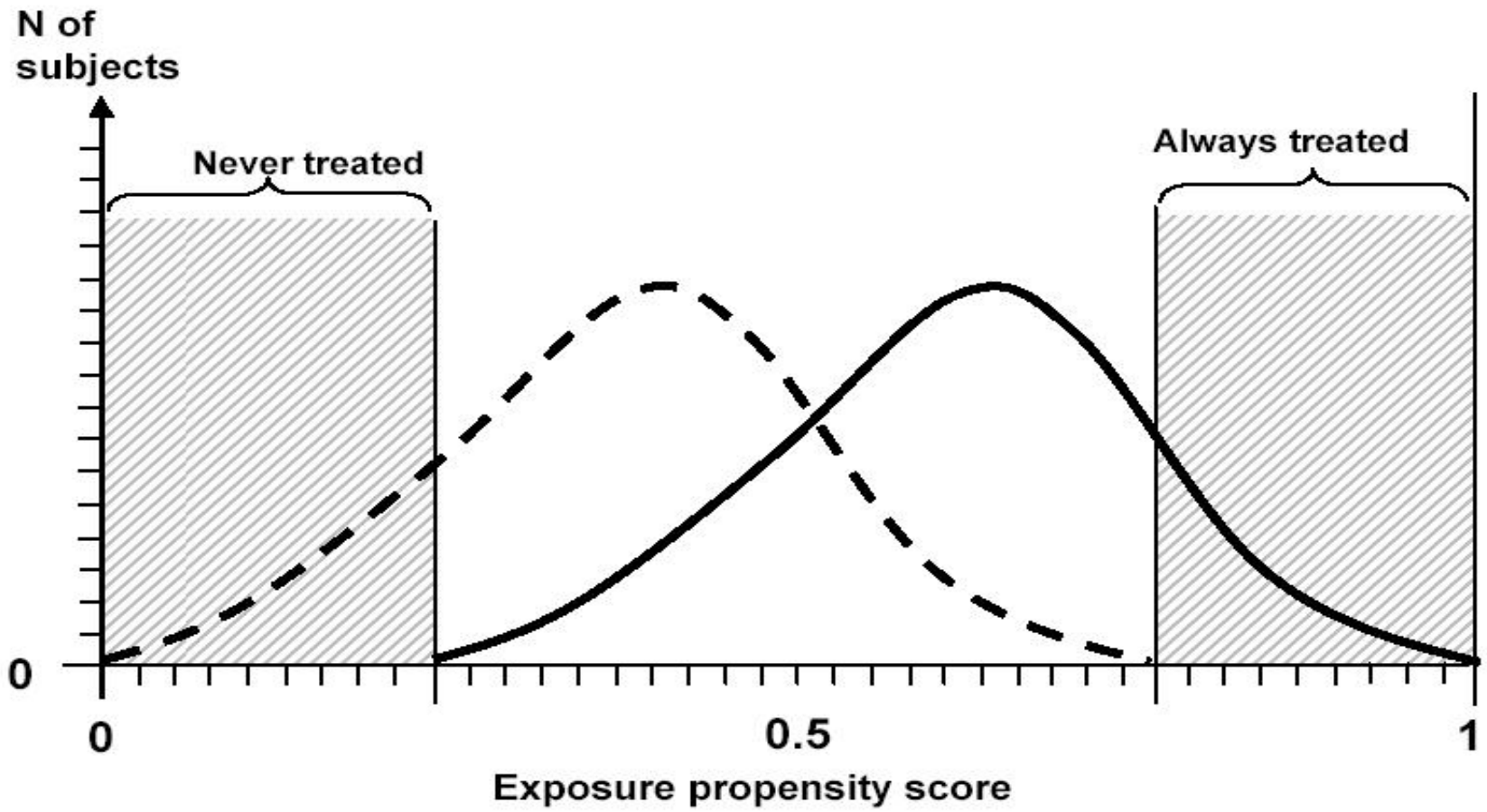

Glynn et al, 2006

“Worst” to Best:

Covariate Adjustment

- Y= B0+ B1*Treatment + B2*PS

Restriction

- Restrict analysis to the cohort that has an overlapping propensity score distribution

Stratification

- Participants divided into score categories (e.g. quintiles)
- Estimates within each strata are created and then summarized

“Worst” to Best:

Inverse-probability-of-treatment-weighting

- Pt who receives treatment is given a weight=ps^{-1}
- Pt who receives no treatment is given a weight=$(1-ps)^{-1}$
- Input the weights in a standard regression
- Estimates the treatment effect in a population whose distribution of risk factors is equal to that found in all study subjects

Matching

- Treated and control patients matched on propensity score
- Mimics a randomized controlled trial by giving each treatment group the same probability of receiving the treatment
- Only accounts for observed covariates

Evaluation of the Matched Group

- Balance, balance, balance

- For baseline covariates:
  - Continuous variables: Paired t-test, Signed rank test
  - Categorical variables: McNemar's test, modified Mantel-Hanszel test

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Results of Multivariable Logistic Regression, Propensity Matching, Propensity Adjustment, and Propensity-based Weighting under Conditions of Nonuniform Effect

Tobias Kurth[1,2,3], Alexander M. Walker[3,4], Robert J. Glynn[1,5,6], K. Arnold Chan[3,4], J. Michael Gaziano[1,2,7], Klaus Berger[8], and James M. Robins[3,6]

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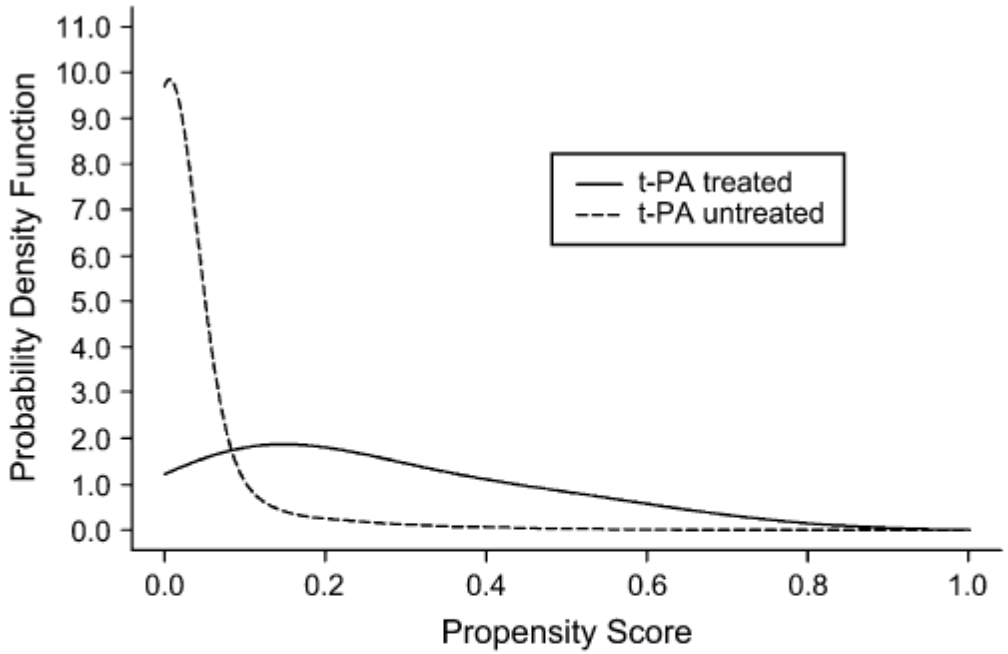

FIGURE 1. Probability density function of the propensity score for the 212 tissue plasminogen activator (t-PA)–treated and the 6,057 t-PA–untreated ischemic stroke patients registered in a German stroke registry between 2000 and 2001.

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Comparison of Methods

	No.	OR*	95% CI*
Crude model	6,269	3.35	2.28, 4.91
Multivariable model†	6,269	1.93	1.22, 3.06
Matched on propensity score	406	1.17	0.68, 2.00
Regression adjusted with propensity score			
Propensity score, continuous	6,269	1.53	0.95, 2.48
Multivariable†	6,269	1.85	1.13, 3.03
Propensity score, deciles	6,269	1.76	1.13, 2.72
Multivariable†	6,269	1.96	1.20, 3.20
Weighted models			
IPTW*	6,269	10.77	2.47, 47.04
SMR* weighted	6,269	1.11	0.67, 1.84

Kurth et al. 2006

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Comparison of Methods

	No.	OR*	95% CI*
Crude model	978	1.36	0.84, 2.19
Multivariable model†	978	1.30	0.74, 2.31
Matched on propensity score	338	0.89	0.49, 1.63
Regression adjusted with propensity score			
Propensity score, continuous	978	0.99	0.58, 1.68
Multivariable†	978	1.29	0.73, 2.29
Propensity score, deciles	978	1.24	0.75, 2.03
Multivariable†	978	1.31	0.74, 2.33
Weighted models			
IPTW*	978	1.09	0.62, 1.93
SMR* weighted	978	0.82	0.47, 1.44

Kurth et al. 2006

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Conclusion from Kurth et al.

- Researchers need to be explicit about population for which the overall treatment estimate is most suitable.

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4 Recommendations for reporting propensity score methods:

1. State matching process (e.g. 1:1)
2. State whether sampling with or without replacement
3. Distribution of baseline covariates in the matched sample compared to the baseline covariates in the unmatched sample
4. Analytical methods used should be appropriate for correlated data

Austin, 2008

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Limitations

- Challenging to include time-varying propensities
  - Initiate, continue or terminate medication use
- Continuous exposures (e.g. dose of medication)
- Multi-categorical exposures
- The propensity score is only as good as the measured variables that go in it.

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Adjunct Systemic Corticosteroid Therapy in Children with Community-Acquired Pneumonia in the Outpatient Setting

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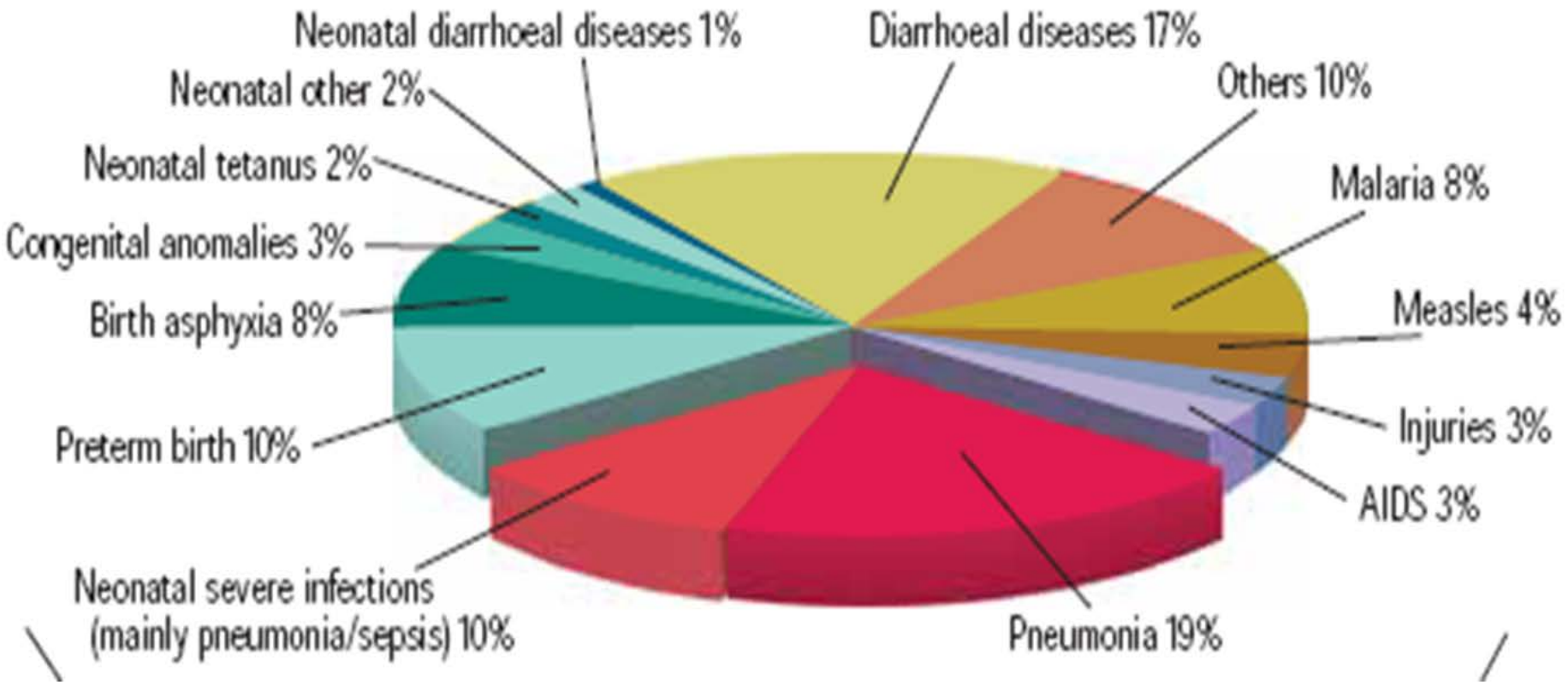
“The Silent Killer”

PNEUMONIA IS THE LEADING KILLER OF CHILDREN WORLDWIDE

Global distribution of cause-specific mortality among children under five, 2004



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Etiology of Community Acquired Pneumonia

- CAP can be caused by a variety of viral and bacterial pathogens (>10 pathogens identified that cause pneumonia)

- Causative agents are diagnosed in <20% of children

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Physiologic Response

- Bacterial pathogens can trigger a complex inflammatory response in the lungs
- An underlying condition of asthma may be exacerbated
- Prescription of adjunct corticosteroid therapy may be useful in inhibiting cytokine release during the inflammatory process

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Objective:

To determine the association between receipt of adjunct corticosteroid therapy and treatment failure in children with community-acquired pneumonia in the outpatient setting.

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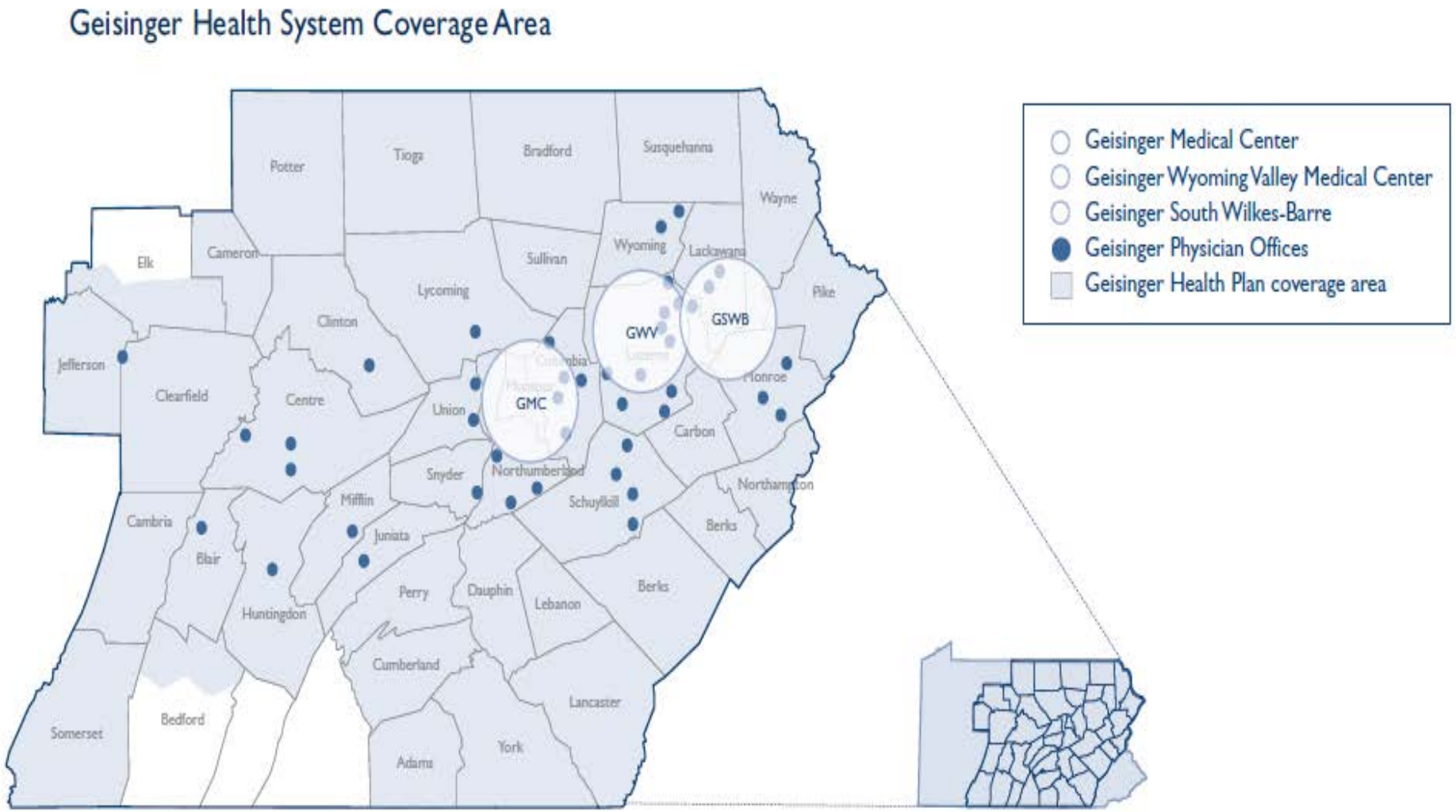
Geisinger Health System



CAP Cohort Selection Criteria

Inclusion Criteria	Exclusion Criteria
Children, 1-18 years	Immunocompromising conditions
Treated within GHS during January 1, 2008 to January 1, 2010	Chronic Medical Conditions other than asthma
Initial diagnosis of CAP in outpatient setting	Patients who did not receive antibiotics when initially diagnosed with CAP, presumed viral pneumonia
	Patients who received antibiotics other than suggested 1st line therapy

Treatment Measure

- Receipt of adjunct systemic corticosteroid therapy at the time of CAP diagnosis

- Methylprednisone, dexamethasone, prednisone, or prednisolone

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Outcome Measure

Treatment Failure: a respiratory-associated follow-up visit accompanied by a change in antibiotic therapy within 14 days of diagnosis in the outpatient, ED, or inpatient settings

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Data Analysis

- Stratification of cohort by asthma status
- Propensity score estimated probability of receiving corticosteroid therapy
- Matched on propensity score within each stratum

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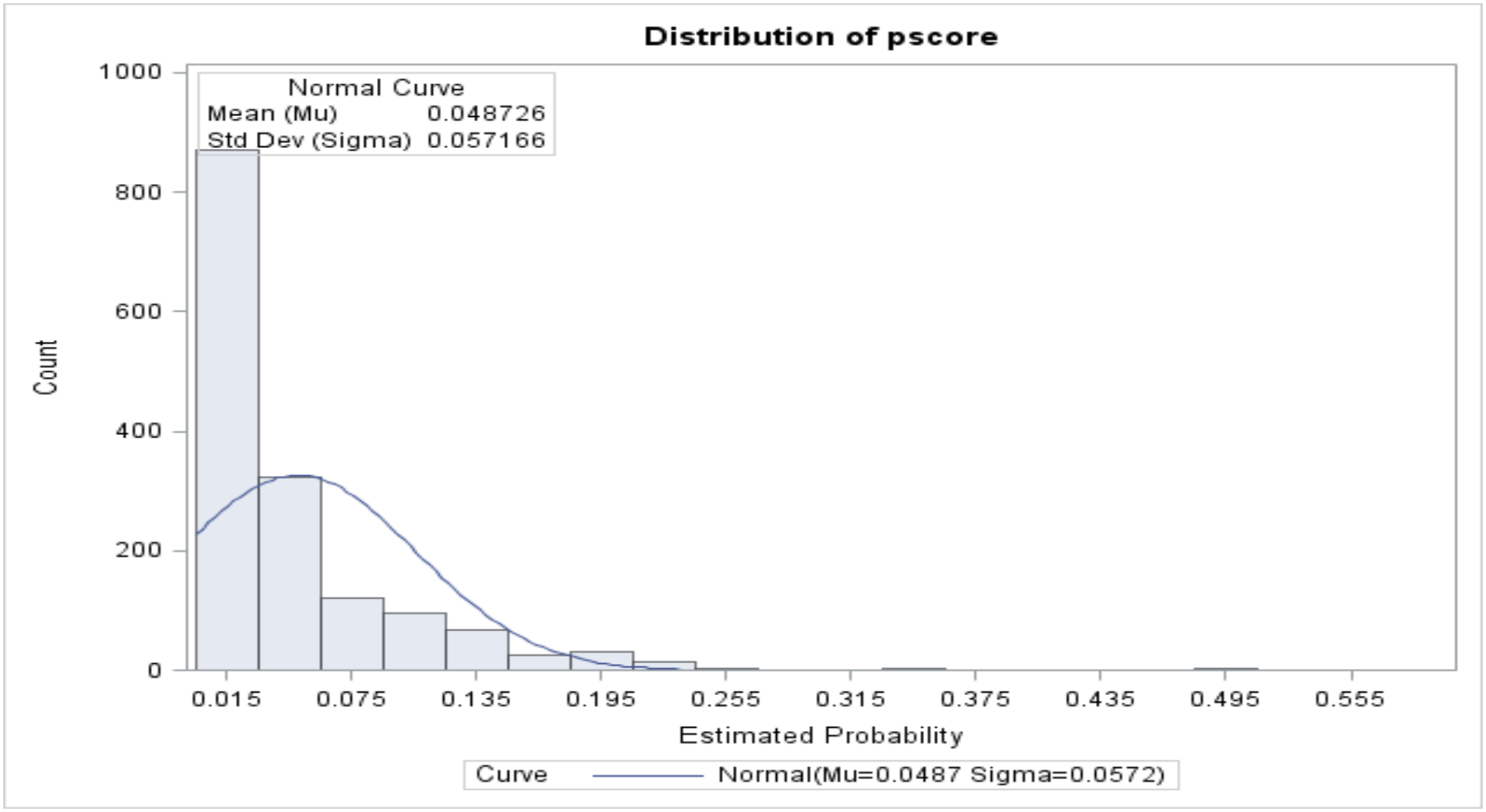
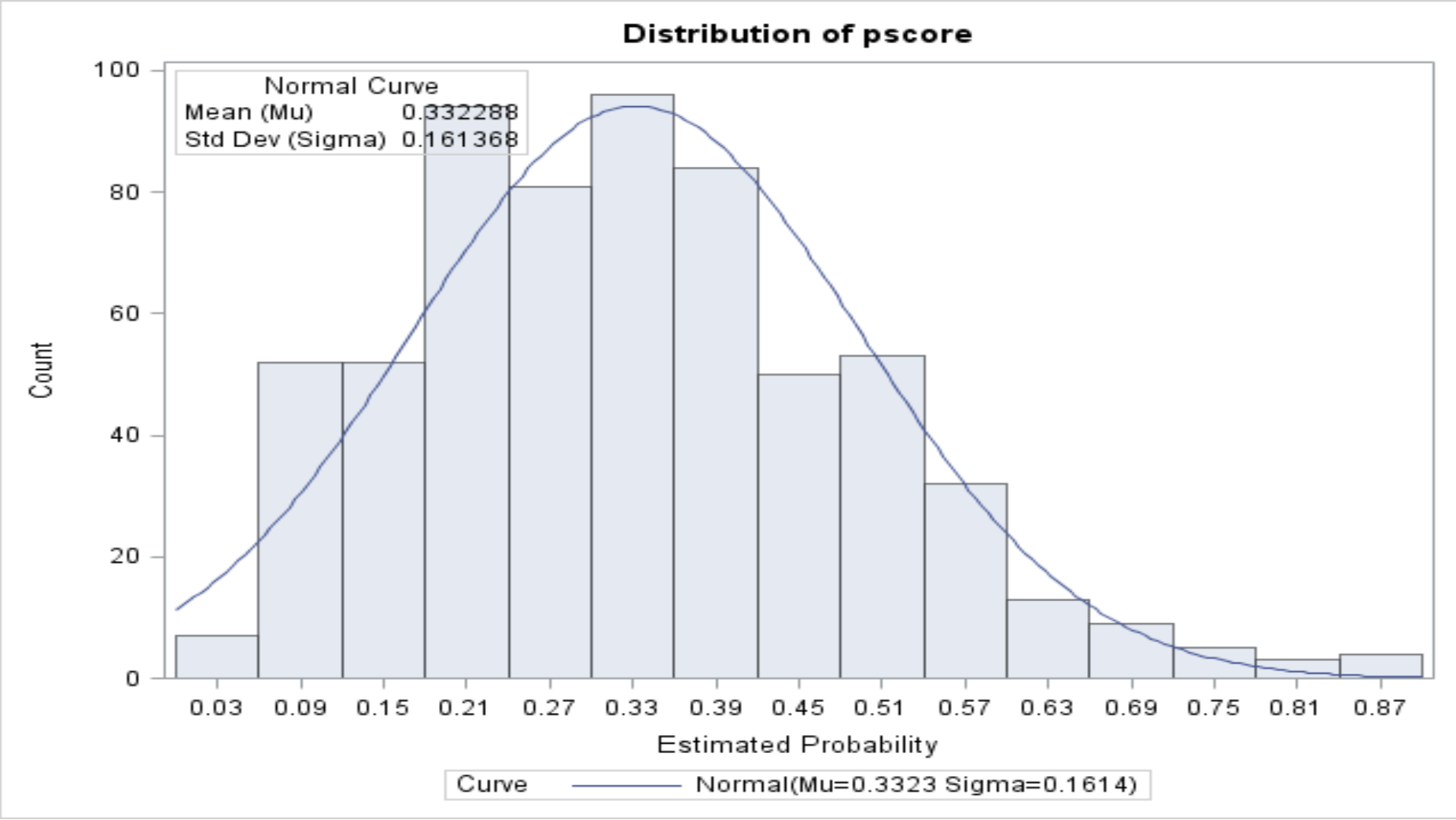
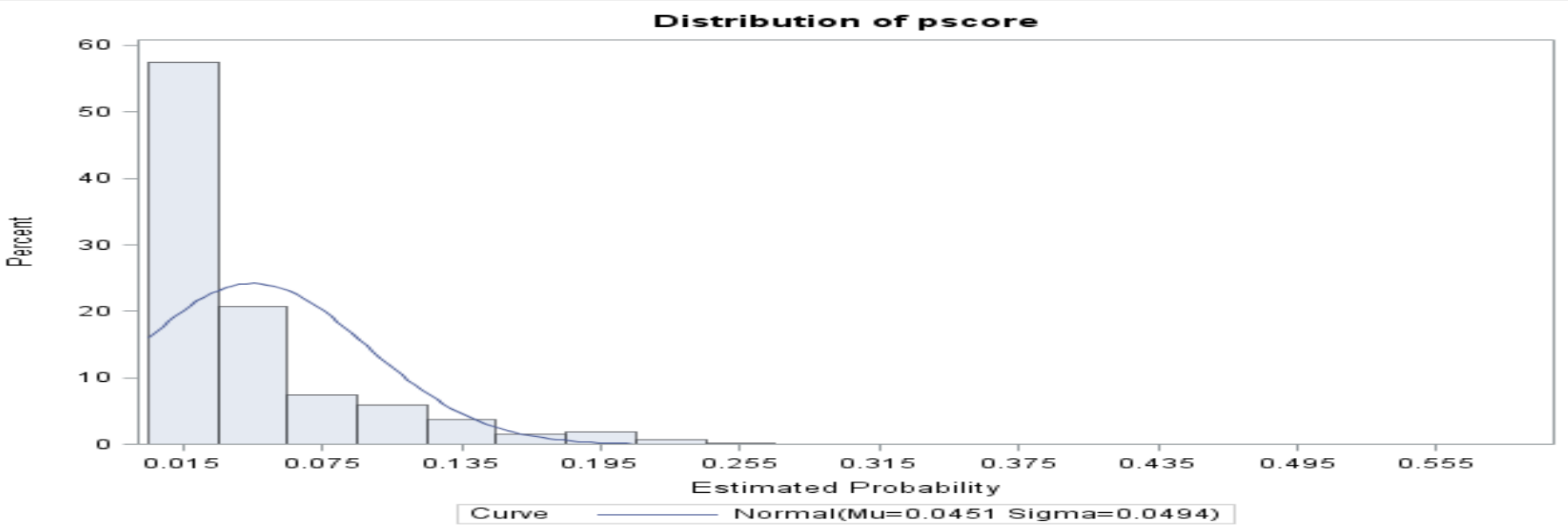
Distribution of Propensity Score in Patients without Asthma

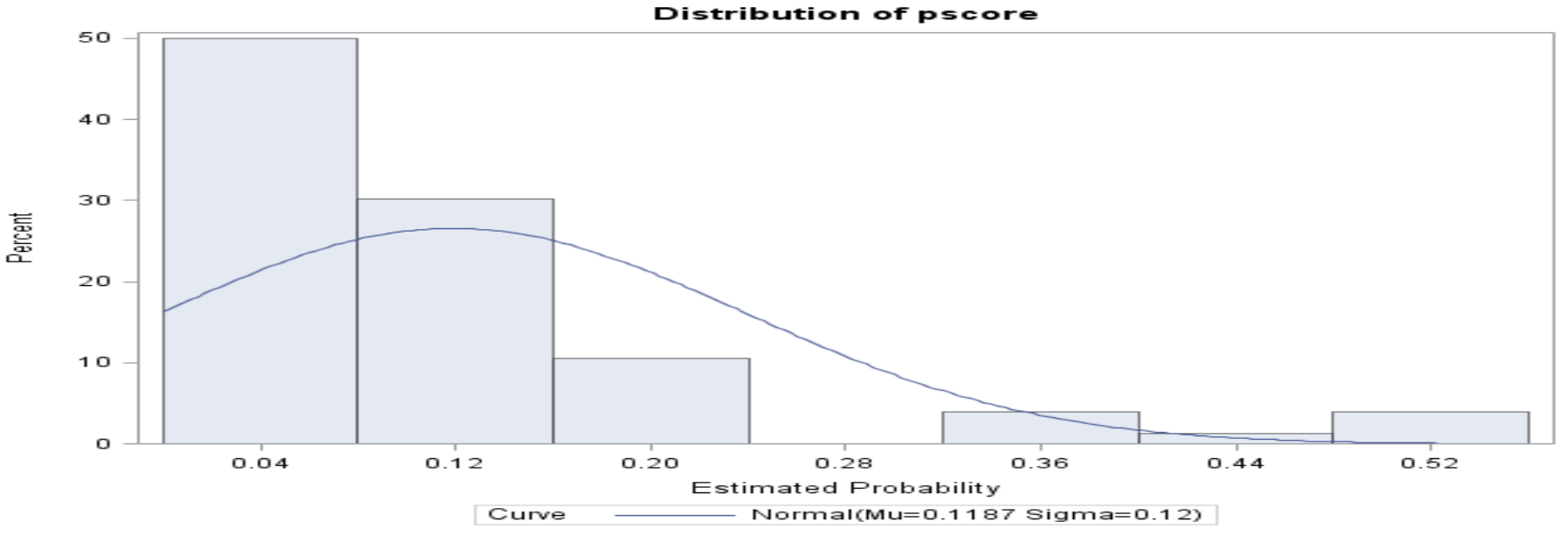


Distribution of Propensity Score in Patients with Asthma

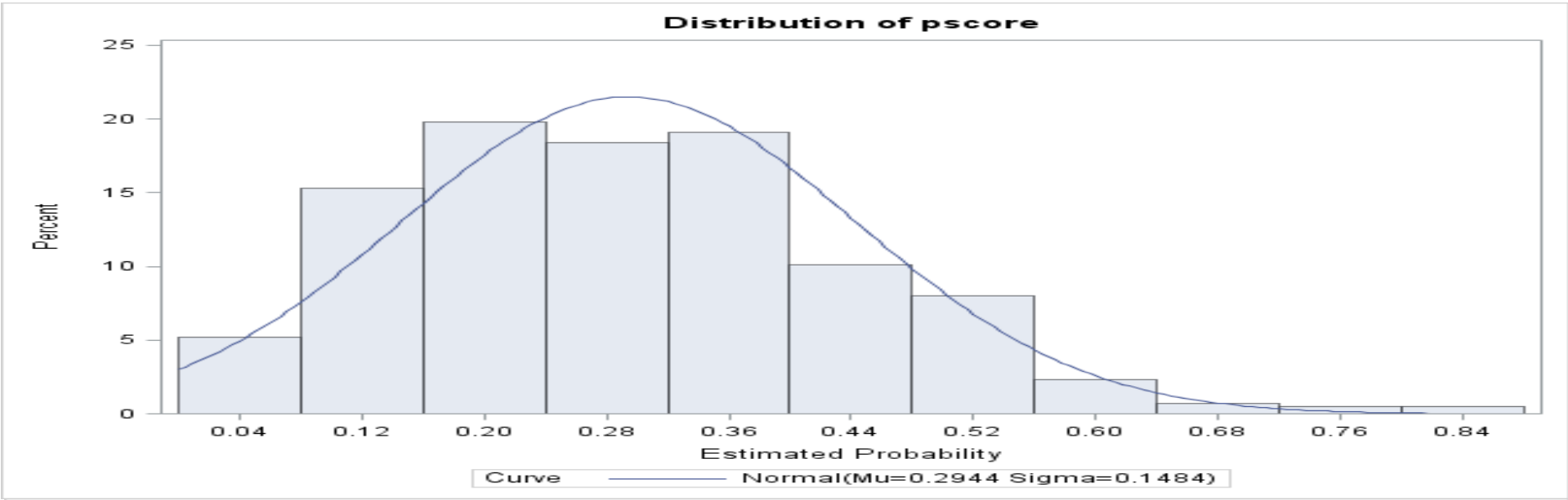


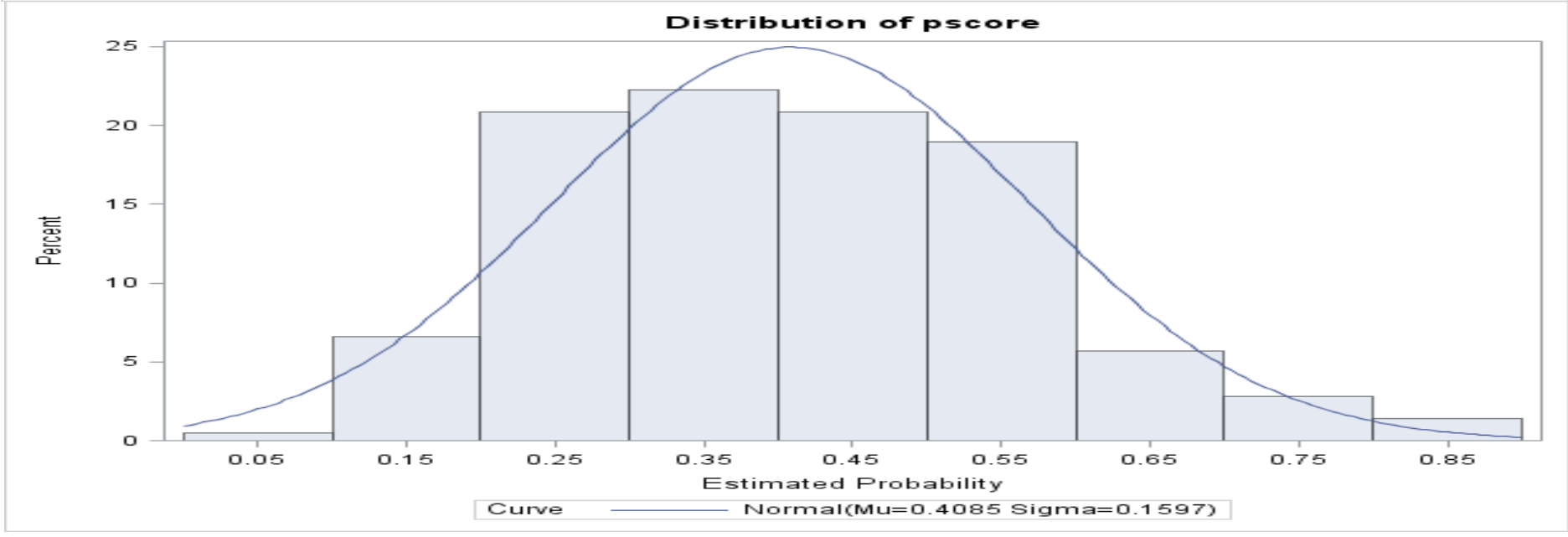
Treatment Distribution among non-Asthma Patients





Treatment Distribution among Asthma Patients





	Total Cohort (n=2244)	Patients with no history of Asthma (n=1589)			Patients with a history of Asthma (n=655)		
Variable Name	n (%)	No Systemic Corticosteroid (n=1513) n, (%)	Systemic Corticosteroid (n=76), n (%)	P-Value	No Systemic Corticosteroid (n=438) n, (%)	Systemic Corticosteroid (n=217), n (%)	P-Value
Age Category							
1-5 y	1032 (46)	728 (48)	38 (50)	0.75	169 (39)	97 (45)	0.13
6-18 y	1212 (54)	785 (52)	38 (50)		269 (61)	120 (55)	
Clinical Signs & Symptoms							
Rales	1202 (54)	858 (57)	34 (45)	0.04	222 (51)	88 (41)	0.01
Wheezing	624 (28)	298 (20)	37 (49)	<0.01	157 (36)	132 (61)	<0.01
Retractions	44 (2)	15 (1)	8 (11)	<0.01	8 (2)	13 (6)	<0.01
Receipt of Albuterol	944 (42)	352 (23)	48 (63)	<0.01	344 (79)	200 (92)	<0.01
Antibiotics Prescribed							
Aminopenicillin	544 (24)	398 (26)	14 (18)	0.03	101 (23)	34 (14)	0.13
2nd Generation Cephalosporin	42 (2)	26 (2)	3 (4)		11 (3)	2 (1)	
3rd Generation Cephalosporin	132 (6)	96 (6)	4 (5)		22 (5)	10 (5)	
Macrolide	1329 (59)	877 (58)	48 (5)		257 (59)	147 (68)	
Aminopenicillin and Macrolide	138 (6)	86 (6)	3 (4)		32 (7)	17 (8)	
2nd Generation Cephalosporin and Macrolide	17 (1)	12 (1)	0		2 (1)	2 (1)	
3rd Generation Cephalosporin and Macrolide	42 (2)	18 (1)	4 (5)		12 (3)	8 (4)	

	Patients with no history of Asthma (n=138)			Patients with a history of Asthma (n=368)		
Variable Name	No Systemic Corticosteroid (n=69) n, (%)	Systemic Corticosteroid (n=69), n (%)	P-Value	No Systemic Corticosteroid (n=184) n, (%)	Systemic Corticosteroid (n=184), n (%)	P-Value
Age Category						
1-5 y	31 (45)	32 (46)	0.86	71 (39)	83 (45)	0.20
6-18 y	38 (55)	37 (54)		113 (61)	101 (55)	
Clinical Signs & Symptoms						
Rales	33 (48)	34 (49)	0.86	77 (42)	83 (45)	0.53
Wheezing	29 (42)	30 (43)	0.86	98 (53)	104 (57)	0.53
Retractions	2 (3)	3 (4)	0.50	5 (3)	5 (3)	1.0
Receipt of Albuterol	38 (55)	41 (59)	0.61	168 (91)	169 (92)	0.85
Antibiotics Prescribed						
Aminopenicillin	19 (28)	14 (20)	0.14	37 (20)	28 (15)	0.77
2nd Generation Cephalosporin	0	3 (4)		2 (1)	2 (1)	
3rd Generation Cephalosporin	1 (1)	3 (4)		8 (4)	9 (5)	
Macrolide	44 (64)	43 (62)		118 (64)	121 (66)	
Aminopenicillin and Macrolide	5 (7)	3 (4)		11 (6)	17 (9)	
2nd Generation Cephalosporin and Macrolide	0	0		1 (1)	2 (1)	
3rd Generation Cephalosporin and Macrolide	0	3 (4)		7 (4)	5 (3)	

Table 3. Treatment Failure by Asthma Status in Matched Cohorts			
	No Systemic Corticosteroids	Systemic Corticosteroids	P-value
Total Cohort	87 (5)	18 (6)	0.20
No Asthma History	2 (3)	8 (12)	0.05
Asthma History	11 (6)	10 (5)	0.82

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Table 4. Odds of failing treatment in patients receiving systemic corticosteroid compared with patients not receiving systemic corticosteroid

	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Receipt of Systemic Corticosteroid*	1.40 (0.83, 2.37)	1.71 (0.78, 3.71)**
No Asthma	2.71 (1.25, 5.88)	4.0 (0.85, 18.84)***
Asthma	0.83 (0.39, 1.78)	0.90 (0.37, 2.22)***

***Reference group is no receipt of corticosteroids**
****Matched within total cohort**
*****Matched within stratified cohort**

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Conclusion

- Adjunct corticosteroid therapy was not associated with an increase of treatment failure among children regardless of asthma status.

- This suggests that in children diagnosed with CAP in the outpatient setting, adjunct corticosteroid therapy may not be beneficial in preventing treatment failure.

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Thank You!

- Samir S. Shah, MD, MSCE
- Maurizio Macaluso, MD, DrPH
- Matt Test, MD

- Campbell Family

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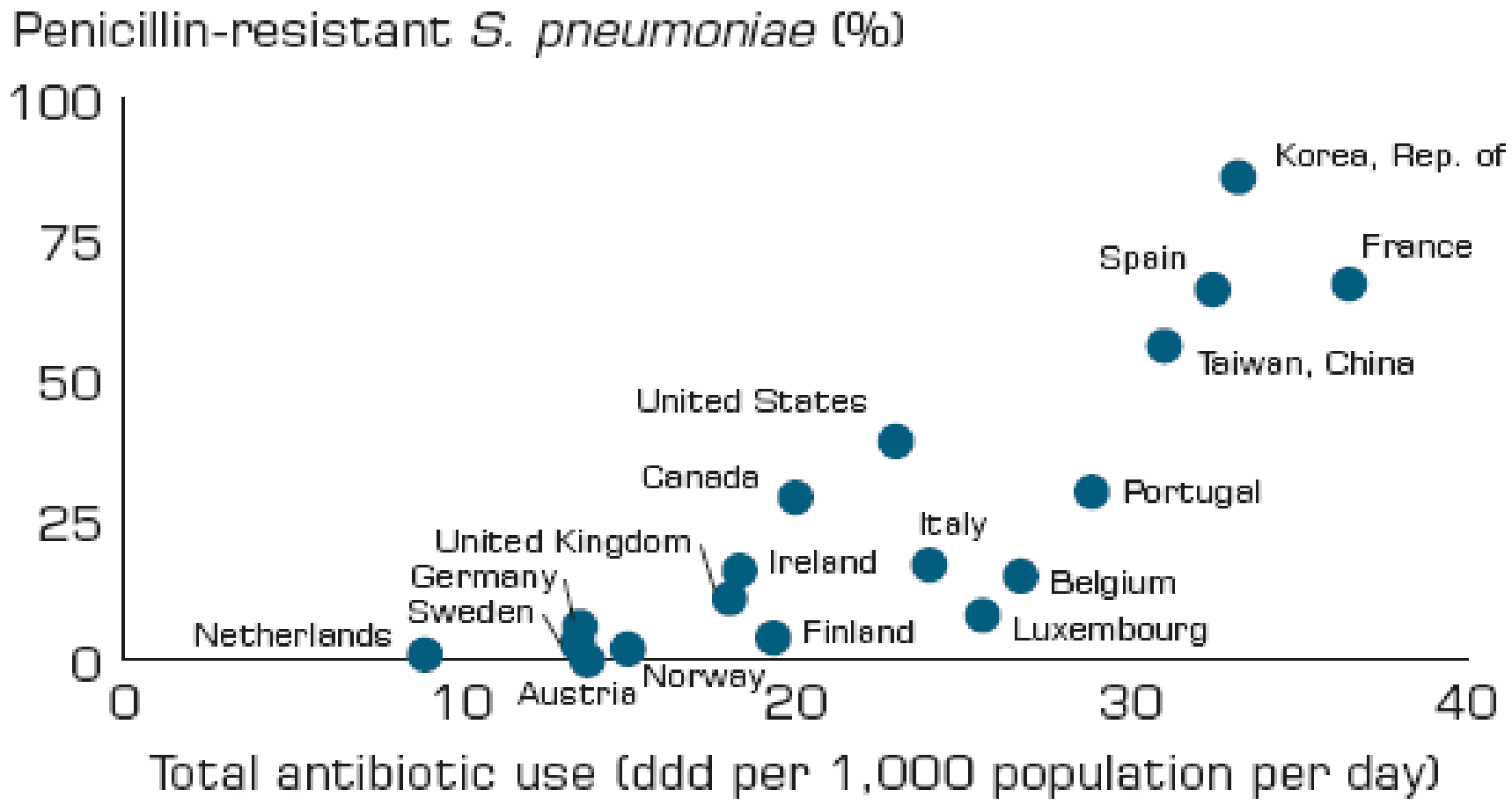
Relationship between penicillin-resistant *S. pneumoniae* and total antibiotic use by country



Note: ddd is defined daily dose.

Source: Albrich, Mannet, and Harbarth (2004).

IDSA/ PIDS Guidelines for the Management

Age of Child	Empiric Therapy for Presumed Bacterial Pneumonia	Empiric Therapy for Presumed Atypical Bacteria
< 5 years old (preschool)	Amoxicillin	Azithromycin
≥ 5 years old	Amoxicillin*	Azithromycin

- If uncertain about etiology of pneumonia, amoxicillin in combination with azithromycin is recommended.
- Reference: Bradley et al. Clin Infect Dis. 2011 Oct; 53(7):e25-76.

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