Stratum-Specific Likelihood Ratios

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Outline

- Last lecture reviewed one categorical approach to interpreting continuous tests: identifying optimal 2x2 table
- Today address second categorical approach to interpreting continuous tests scores: development of stratum-specific likelihood ratios (SSLR)
- In what follows:
  - Describe construction of SSLR
  - Demonstrate calculation of post-test probabilities by use of SSLR (you already know how)
  - Describe relationship between SSLR and ROC curve
  - Discuss relationship between LR+ and LR- and ROC curve

2x2 Approach

- In 2x2 approach to continuously scaled tests, aggregate data into a series of cumulative 2x2 tables

Cut-off	Children w/ Bacteremia	Children w/o Bacteremia
≥25	6	26
≥20, <25	4	43
≥15, <20	7	129
≥10, <15	7	292
≥0, <10	2	369

Cut-off	Children w/ Bacteremia	Children w/o Bacteremia
≥25	6	26
≥20, <25	4	43
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≥25	6	26
≥20, <25	4	43
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≥10, <15	7	292
≥0, <10	2	369

SSLR Approach

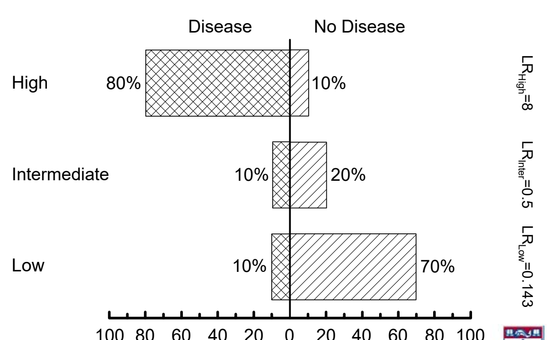
- In SSLR approach, calculate likelihood ratios for particular test results or ranges of test results (i.e., strata) and never aggregate results of one stratum with those of another
- Strata can be large -- like five used to summarize WBC data – or can be infinitesimally small
  - e.g., if we plot the distribution of positive test scores and the distribution of negative test scores, we can define likelihood ratios for every point on the two curves

Formula for LR_i

- SSLR: Fraction of diseased individuals with a test result (or a test result in a particular range) divided by fraction of nondiseased individuals with a test result (or a test result in same range)
- Generalization of formula for a likelihood ratio for test $result_i$ is as follows:

$$LR_i = \frac{\text{Probability of test result i given D+}}{\text{Probability of test result i given D-}}$$

Graphical Interpretation of SSLR



High: 8; Intermediate: 0.5; Low: 0.143

Three Methods for the Calculatint SSLR

- At least 4 methods for calculating SSLR
- All 4 are transformations of one another
  - Except for possible differences due to rounding, all 3 yield exact same results
- For all 4 methods, first step is to establish strata and tabulate stratum specific test results
  - Continue to illustrate the principles by use of data about white blood cell (WBC) counts for the diagnosis of bacteremia

Method 1: Use Stata CSI Program

- Use same csi program we used in lecture 2 to identify LR+/LR- and their 95% CI

Stratum	Bact (a)	No Bact (b)	SSLR
$\geq$25	**6**	**26**	
$\geq$20, <25	4	43	
$\geq$15, <20	7	129	
$\geq$10, <15	7	292	
$\geq$0, <10	2	369	
Total	26 (e)	859 (f)	--

* Same calculations we used for slopes of ROC curve

Stata Command for $LR_{\geq 25}$

csi 6 26 20 833 (csi N_{TP} N_{FP} N_{FN} N_{TN})

	Exposed	Unexp	Total	
Cases	6	26	32	
Noncases	20	833	853	
Total	26	859	885	
Risk	.2307692	.0302678	.0361582	
	Point Estimate		95% Conf. Interval	
Risk diff	.2005015		.0381476	.3628554
Risk ratio	**7.62426**		**3.434883**	**16.2766**
Attr frac ex	.8688397		.7088692	.9409097
Attr frac pop	.1629075			

chi2(1) = 29.11 Pr>chi2 = 0.0000

Exposed = D+; Cases = T+ Unexposed = D-; Noncases = T-

SSLR for ≥20, <25

Stratum	Bact (a)	No Bact (b)	SSLR
≥25	6	26	7.62426
≥20, <25	**4**	**43**	
≥15, <20	7	129	
≥10, <15	7	292	
≥0, <10	2	369	
Total	26 (e)	859 (f)	--

Stata Command for CI for $LR_{\geq 20:<25}$

csi 4 43 22 816

	Exposed	Unexp	Total	
Cases	4	43	47	
Noncases	22	816	838	
Total	26	859	885	
Risk	.1538462	.0500582	.0531073	
	Point Estimate		95% Conf. Interval	
Risk diff	.1037879		-.0356616	.2432375
Risk ratio	**3.073345**		**1.191737**	**7.925783**
Attr frac ex	.6746217		.160889	.8738295
Attr frac pop	.0574146			

chi2(1) = 5.41 Pr>chi2 = 0.0201

Exposed = D+; Cases = T+ Unexposed = D-; Noncases = T-

Method 1: All SSLR…

Stratum	Bact (a)	No Bact (b)	SSLR
≥25	6	26	7.62426
≥20, <25	4	43	3.07335
≥15, <20	7	129	1.79279
≥10, <15	7	292	0.79202
≥0, <10	2	369	0.17907
Total	26 (e)	859 (f)	--

Method 2: (axf) / (bxe) *

- Use extension of the (axf) / (b*e) method we used to calculate LR+ / LR-

Stratum	Bact (a)	No Bact (b)	(a*f) / (b*e)	
≥25	6	26		
≥20, <25	4	43		
≥15, <20	7	129		
≥10, <15	7	292		
≥0, <10	2	369		
Total	26 (e)	859 (f)	--	--

* Same calculations we used for slopes of ROC curve

Method 2: (axf) / (bxe), $LR_{\geq 25}$

Stratum	Bact	No Bact	(axf) / (bxe)	SSLR
≥25	6	26	(6x859) / (26x26)	7.62426
≥20, <25	4	43		
≥15, <20	7	129		
≥10, <15	7	292		
≥0, <10	2	369		
Total	26	859	--	--

Method 2: (axf) / (bxe), $LR_{\geq 20, <25}$

Stratum	Bact	No Bact	(axf) / (bxe)	SSLR
≥25	6	26	(6x859) / (26x26)	7.62426
≥20, <25	4	43	(4x859) / (43x26)	3.07335
≥15, <20	7	129		
≥10, <15	7	292		
≥0, <10	2	369		
Total	26	859	--	--

Method 2: (axf) / (bxe)

- All SSLR

Stratum	Bact	No Bact	(axf) / (bxe)	SSLR
>25	6	26	(6x859) / (26x26)	7.62426
>20, <25	4	43	(4x859) / (43x26)	3.07335
>15, <20	7	129	(7x859) / (129x26)	1.79279
>10, <15	7	292	(7x859) / (292x26)	0.79202
>0, <10	2	369	(2x859) / (369x26)	0.17907
Total	26	859	--	--

* As previously noted, SSLR = slopes of ROC curve

CI for Method 2

- Use csi to calculate approximate confidence intervals

Stratum	SSLR	95% CI
>25	7.6243	3.435 to 16.923
>20, <25	3.0733	1.192 to 7.926
>15, <20	1.7928	0.933 to 3.444
>10, <15	0.7920	0.418 to 1.502
>0, <10	0.1791	0.047 to 0.680

>25: csi 6 26 20 833
>20, <25: csi 4 43 22 816
>15, <20: csi 7 129 19 730

csi a b (e-a) (f-b)

SSLR VS LR+/LR-

SSLR Approach		2x2 Approach *		
Cut-off	SSLR	Cut-off	LR+	LR-
--	--	All Neg	--	1
>25	**7.6243**	>25	**7.6243**	0.7932
>20,<25	3.0733	>20	4.7882	0.6690
>15,<20	1.7928	>15	2.8336	0.4498
>10,<15	0.7920	>10	1.6182	**0.1791**
<10	**0.1791**	All Pos	1	--

* LR+/LR- from Lecture 2

Method 3. Percentiles

- Compute proportion of patients with disease with 5 results

Stratum	Bact	No Bact	% Bact
≥25	6	26	0.23077
≥20, <25	4	43	0.15385
≥15, <20	7	129	0.26923
≥10, <15	7	292	0.26923
≥0, <10	2	369	0.07692
Total	26	859	1.000

Method 3. Percentiles

- Compute proportion of patients without disease with 5 results

Stratum	Bact	No Bact	% Bact	% No Bact
≥25	6	26	0.23077	0.03027
≥20, <25	4	43	0.15385	0.05006
≥15, <20	7	129	0.26923	0.15017
≥10, <15	7	292	0.26923	0.33993
≥0, <10	2	369	0.07692	0.42957
Total	26	859	1.000	1.000

Method 3. Percentiles

- Step 4. Divide the fractions with disease by the fractions without disease

Stratum	Bact	No Bact	% Bact	% No Bact	SSLR
≥25	6	26	0.23077	0.03027	7.6237 *
≥20, <25	4	43	0.15385	0.05006	3.0733
≥15, <20	7	129	0.26923	0.15017	1.7928
≥10, <15	7	292	0.26923	0.33993	0.7920
≥0, <10	2	369	0.07692	0.42957	0.1791
Total	26	859	1.000	1.000	--

* Difference due to rounding

Method 4: Differences in Sensitivities and 1-Specificities

Stratum	Sens	1-Spec
$\geq\infty$	0	0
$\geq$25	0.23077	0.03027
$\geq$20	0.38462	0.08033
$\geq$15	0.65385	0.23050
$\geq$10	0.92308	0.57043
$\geq$0	1.00000	1.00000

Method 4. $(Se_{j=i} - Se_{j=i-1})/(1-Sp_{j=i} - 1-Sp_{j=i-1})$

Stratum	$Se_{j=i} - Se_{j=i-1}$		$1-Sp_{j=i} - 1-Sp_{j=i-1}$	Slope
$\geq$25	0.23077 - 0.00000	/	0.03027 - 0.00000	7.6237 *
$\geq$20, <25	0.38462 - 0.23077	/	0.08033 - 0.03027	3.0733
$\geq$15, <20	0.65385 - 0.38462	/	0.23050 - 0.08033	1.7928
$\geq$10, <15	0.92308 - 0.65385	/	0.57043 - 0.23050	0.7920
$\geq$0, <10	1.00000 - 0.92308	/	1.00000 - 0.57043	0.1791

* Difference due to rounding

SSLR and Post-Test Probabilities

- SSLR greater than 1 indicate test result occurs more frequently when disease is present than when it is absent
- When considering 2 outcomes, SSLR>1 yield post-test probabilities greater than pre-test probabilities
  - All else equal, the larger the SSLR, the greater the shift between pre- and post-test probabilities

SSLR and Post-Test Probabilities (2)

- SSLR less than 1 indicate test result occurs less frequently when disease is present than when it is absent
- When considering 2 outcomes, SSLR<1 yield post-test probabilities less than pre-test probabilities
  - All else equal, the smaller the SSLR, the greater the shift between pre- and post-test probabilities
- SSLR that equal 1 yield post-test probabilities that equal pre-test probabilities (i.e., no information)

SSLR and the Calculation Of Post-test Probability Of Disease

- Of five methods we introduced to calculate post-test probability of disease, three used likelihood ratios:
  - Odds transformation method
  - Likelihood ratio and probability method
  - Nomogram
- Can use any of these three methods to calculate post-test probabilities by use of SSLR
- Below, use likelihood ratio and probability method

$$\frac{\text{Pre-test probability * } LR_i}{(\text{Pre-test probability * } LR_i) + (1\text{-Pre-test probability})}$$

Post-Test Probabilities

- If pre-test probability of bacteremia of 10%, post-test probabilities of bacteremia equal:

$\geq$25 $$\frac{0.1 * 7.6243}{(0.1 * 7.6243) + 0.9} = \frac{0.76243}{1.66243} = 0.459$$

$\geq$20, <25 $$\frac{0.1 * 3.0733}{(0.1 * 3.0733) + 0.9} = \frac{0.30733}{1.20733} = 0.255$$

$\geq$15, <20 $$\frac{0.1 * 1.7928}{(0.1 * 1.7928) + 0.9} = \frac{0.17928}{1.07928} = 0.161$$

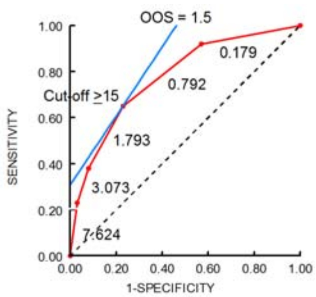
$\geq$10, <15 $$\frac{0.1 * 0.7929}{(0.1 * 0.7929) + 0.9} = \frac{0.07929}{0.97929} = 0.081$$

<10 $$\frac{0.1 * 0.1791}{(0.1 * 0.1791) + 0.9} = \frac{0.01791}{0.91791} = 0.020$$

Identifying “Positive” and “Negative” SSLR

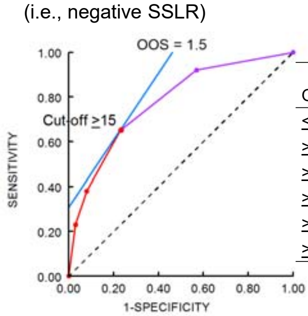
How Do We Identify Positive Test Results?

- Is there something algebraic about ROC curve that is related to SSLR AND associated with positive and negative test results?



SSLR/Slopes of ROC Curve < OOS

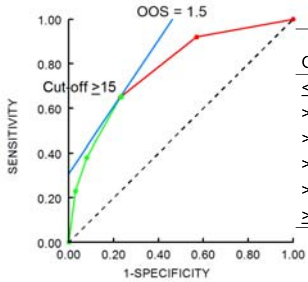
- SSLR/ROC curve slopes less than OOS (violet line segments) represent strata with negative test results (i.e., negative SSLR)



OOS	“Negative” SSLR
≤0.179	None
≥0.179; <0.792	≤0.179
≥0.792; <1.793	≤0.792
≥1.793; <3.073	≤1.793
≥3.073; <7.624	≤3.073
≥7.624	All

SSLR/Slopes of ROC Curve > OOS

- SSLR/ROC curve slopes greater than OOS (green line segments) represent strata with positive test results (i.e., positive SSLR)



OOS	"Positive" SSLR
≤0.179	All
>0.179; ≤0.792	≥0.792
>0.792; ≤1.793	≥1.793
>1.793; ≤3.073	≥3.073
>3.073; ≤7.624	≥7.624
≥7.624	None

Can identify "positive" and "Negative" SSLR by comparing OOS and SSLR (which equal slopes of ROC curve)

Strata with SSLR < OOS represent "negative" SSLR; those with SSLR > OOS represent "positive" SSLR; those with SSLR = OOS represent either "positive" or "negative" SSLR

Implication

- Can determine stratum specific results that are "positive" by comparing OOS and SSLR
- Because optimal 2x2 table includes all positive strata (future proof), can identify optimal 2x2 table by making same comparison
- Does not mean SSLR fully replace sensitivity and specificity

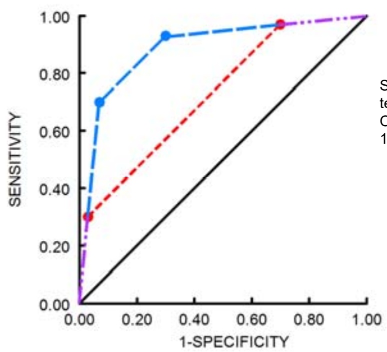
SSLR "Throw Away" Information in 2x2 Table

- Can identify cut-off for positive test and "positive" SSLR without ROC curve
- But SSLR "throw away" other information contained in ROC curve that is useful for decisions such as choice between tests
- Suppose 2 tests have
  - Same number of strata
  - Same SSLR (0.1, 1, and 10)
  - All else (test cost,risk, delay, etc.) equal

Can 1 test be better than the other?

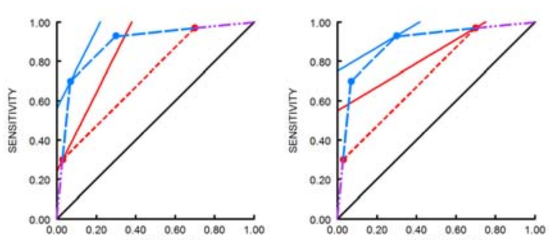
If so, are SSLR sufficient for determining which test is better?

SSLR Alone Not Sufficient for Choice



SSLR for both tests: 10, 1, 0.1
Operating Points: 1-spec, sens
Red test
0.03, 0.30
0.70, 0.97
Blue test
0.07, 0.70
0.30, 0.93

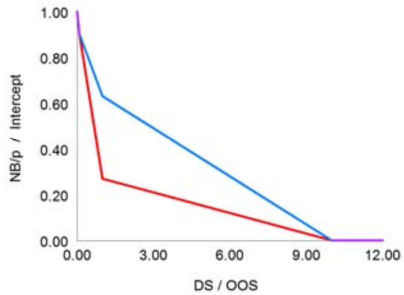
For All OOS, Blue Test Has Larger or Equal Intercepts



OOS = 2 and 0.6,respectively

Plot of Intercepts for Red and Blue Tests

- Rotate OOS from 0 to ... (in this example, 12); plot resulting intercepts of lines tangent to blue and red tests



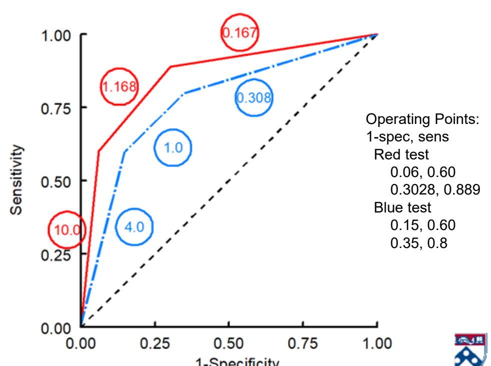
SSLR "Throw Away" Information (2)

- Suppose 2 tests have same number of strata
- But test 1's SSLR all more indicative of having or not having disease (i.e., "better") than test 2's SSLR

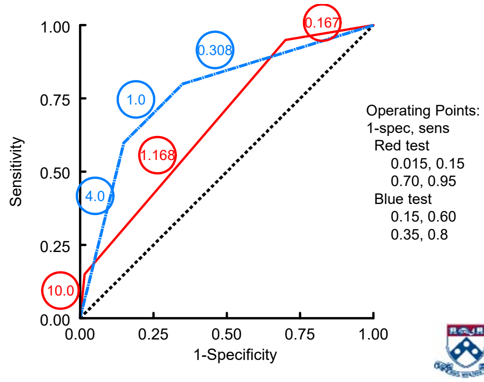
	SSLR	
Test result	Test 1	Test2
High	10	4
Medium	1.168	1
Low	0.167	0.308

- Is test 1 better than test 2?
- If so, do SSLR alone provide information we need to choose between tests?

Test with "Better" SSLR Can Be Better…



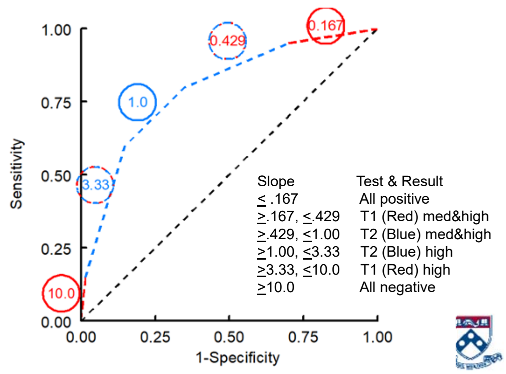
But "Better" SSLR Neither Necessary Nor Sufficient



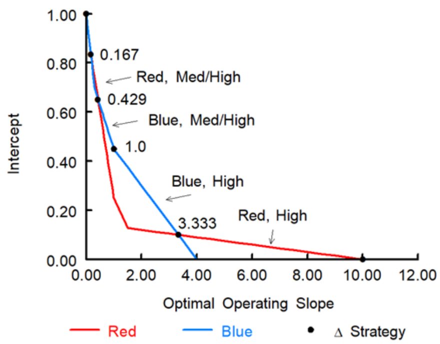
Test with "Better" SSLR Not Necessarily Better Because…

- …Predictive ability depends on both:
  - Magnitude of LR
  - Fraction of patients in whom LR will be used
- In example:
  - LR for test 1's "high" result (10) greater than LR for test 2's high result (4)
  - But test 1's high result occurs in only 15% (red sens) of patients with disease, while test 2's "high" result occurs in 60% (blue sens) of patient's with disease
- Difference in frequency means for some pretest probabilities use of test 2's high result (with smaller LR) more appropriate than use of test 1's high result

OSS Indicates Appropriate Test and Cut-off



Plot of Intercepts for Red and Blue Tests



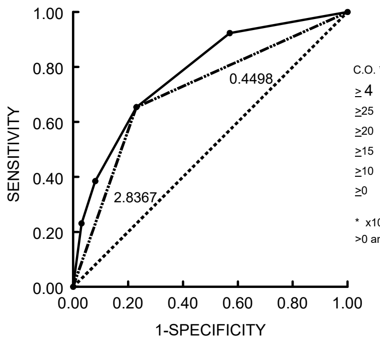
LR+ and LR- and ROC Curves

- There are also relationships between LR+, LR- and ROC curves
- LR+ equals sensitivity / (1-specificity)
- Points on the ROC curve equal sensitivity and 1-specificity of each of the plotted 2x2 tables
- Thus slope of line drawn from the origin to any point on the ROC curve equals the LR+ for the 2x2 table that is represented by the point

LR+ and LR- and ROC Curves (2)

- Similarly, LR- equals (1-sensitivity) / specificity
- Change in sensitivity between the point on the ROC curve and the upper right corner of the ROC curve (1,1) equals 1-sensitivity
- Change in 1-specificity between the point on ROC curve and upper right corner of the ROC curve equals specificity
- Thus, slope of line between a point on the ROC curve and the upper right corner of ROC curve equals (1-sensitivity) / specificity, or LR-

LR+ and LR- and ROC Curves (3)



C.O. *	SENS	1-SPEC
≥ 4	0.000	0.000
≥25	0.231	0.030
≥20	0.385	0.080
≥15	0.654	0.231
≥10	0.923	0.570
≥0	1.000	1.000

* x1000/mm³; Cells >0 and >5 combined

SSLR and ΔO_{D+} and ΔO_{D-}

- Does use of SSLR imply we needn't be concerned with ΔO_{D+} and ΔO_{D-}?
  - Yes when we are calculating the post-test probability of disease
  - No when we are using test result to make a treatment decision

Summary

- Introduced stratum specific likelihood ratios, which are extensions of LR+ and LR- to multilevel/continuous test results
- Demonstrated 3 methods for calculating SSLR
- Demonstrated 1 of 3 methods for using SSLR to calculate post-test probabilities of disease
  - Methods are generalizations of methods introduced in 2x2 module when we described LR+ and LR-
- Also described relationship between SSLR and slopes of ROC curve, and indicated that comparison of optimal operating slope to SSLR, allows identification of optimal positive test cut-off for a particular patient or class of patients

Appendix
VQ-Scanning Worked Example

PIOPED SSLR Example *

Ventilation-Perfusion (V/Q) scanning

Result	# W/Dis (a)	# W/O Dis (b)
High Prob	102	14
Intermed	105	217
Low Prob	39	273
Normal	5	126
Total	251 (e)	630 (f)

* Jaeschke, JAMA, 1994;271:703-7

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 1

Result	(“A” x ”F”)	/	(“B” x “E”)	SSLR
High Prob				
Intermed				
Low Prob				
Normal				

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 1

Result	(“A” x ”F”)	/	(“B” x “E”)	SSLR
High Prob	(102* x 630)	/		
Intermed	(105 x 630)	/		
Low Prob	(39 * 630)	/		
Normal	(5 * 630)	/		

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 1

Result	(“A” x ”F”)	/	(“B” x “E”)	SSLR
High Prob	(102* x 630)	/	(14 x 251)	
Intermed	(105 x 630)	/	(217 x 251)	
Low Prob	(39 * 630)	/	(273 * 251)	
Normal	(5 * 630)	/	(126 * 251)	

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 1

Result	(“A” x ”F”)	/	(“B” x “E”)	SSLR
High Prob	(102* x 630)	/	(14 x 251)	18.287
Intermed	(105 x 630)	/	(217 x 251)	1.214
Low Prob	(39 * 630)	/	(273 * 251)	0.359
Normal	(5 * 630)	/	(126 * 251)	0.100

PIOPED SSLR Example *

Ventilation-Perfusion (V/Q) scanning

- Approach 2

Result	N	% W/Dis	N	% W/O Dis	SSLR
High Prob	102		14		
Intermed	105		217		
Low Prob	39		273		
Normal	5		126		
Total	251		630		

* Jaeschke, JAMA, 1994;271:703-7

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 2

Result	N	% W/Dis	N	% W/O Dis	SSLR
High Prob	102	.4064	14		
Intermed	105	.4183	217		
Low Prob	39	.1554	273		
Normal	5	.0199	126		
Total	251	1.00	630		

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 2

Result	N	% W/Dis	N	% W/O Dis	SSLR
High Prob	102	.4064	14	.0222	
Intermed	105	.4183	217	.3444	
Low Prob	39	.1554	273	.4333	
Normal	5	.0199	126	.2000	
Total	251	1.00	630	1.00	

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 2

Result	N	% W/Dis	N	% W/O Dis	SSLR
High Prob	102	.4064	14	.0222	18.31
Intermed	105	.4183	217	.3444	1.215
Low Prob	39	.1554	273	.4333	0.359
Normal	5	.0199	126	.2000	0.100
Total	251	1.00	630	1.00	--

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 3

Result	$Se_{j=i+1}$-$Se_{j=i}$	/	(1-$Sp_{j=i+1}$-1-$Sp_{j=i}$)	SSLR
High Prob				
Intermed				
Low Prob				
Normal				

PIOPED SSLR Example

Ventilation-Perfusion (V/Q) scanning

- Approach 3

Result	$Se_{j=i+1}$-$Se_{j=i}$	/	(1-$Sp_{j=i+1}$-1-$Sp_{j=i}$)	SSLR
High Prob	.40637-.00000			
Intermed	.82470-.40637			
Low Prob	.98008-.82470			
Normal	1.0000-.98008			

PIOPED SSLR Example

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Result	$Se_{j=i+1}$-$Se_{j=i}$	/	(1-$Sp_{j=i+1}$-1-$Sp_{j=i}$)	SSLR
High Prob	.40637-.00000		.02222-.00000	
Intermed	.82470-.40637		.36667-.02222	
Low Prob	.98008-.82470		.80000-.36667	
Normal	1.0000-.98008		1.0 - .80	

PIOPED SSLR Example

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Result	$Se_{j=i+1}$-$Se_{j=i}$	/	(1-$Sp_{j=i+1}$-1-$Sp_{j=i}$)	SSLR
High Prob	.40637-.00000		.02222-.00000	18.288
Intermed	.82470-.40637		.36667-.02222	1.214
Low Prob	.98008-.82470		.80000-.36667	0.359
Normal	1.0000-.98008		1.0 - .80	0.100