Comparing the assessments of treatment response to proton pump inhibitors for Laryngo-Pharyngeal reflux disease between patients and clinicians

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Background

Laryngo-Pharyngeal Reflux Disease (LPRD)

- The most common symptoms are non-specific, such as cough, foreign body sensation, throat clearing, sore throat, dysphagia, hoarseness, dysphonia, etc.
- There is no clear diagnosis, and the prevalence of LPRD is unknown.
- No clear pathogenesis to explain the cause of LPRD symptoms.
- Main treatment: **Proton Pump Inhibitor (PPI)**

Diagnosis

Gastroscopy	• The sensitivity is not high.
24 hr-pH monitoring	• The most stringent diagnostic criteria, but it is a 24-hr invasive examination, and the sensitivity is not high, so the patient acceptance is low.
Therapeutic trial	• Direct treatment such as PPI for 2 to 3 months and observe the treatment response
Reflux Finding Score (RFS)	• The signs that may be observed in the throat by fiberoptic endoscopic examination are summarized into 8 indicators and scored.

Abnormal: RSI ≥ 13 or RFS ≥ 7

Index

Reflux Symptom Index (RSI)

1. Hoarseness or a problem with your voice.
2. Clearing your throat.
3. Excess throat mucus or postnasal drip.
4. Difficulty swallowing food, liquids, or pills.
5. Coughing after you ate or after lying down.
6. Breathing difficulties or choking episodes.
7. Troublesome or annoying cough.
8. Sensations of something sticking in your throat or a lump in your throat.
9. Heartburn, chest pain, indigestion, or stomach acid coming up.

Score: 0 = No Problem ~ 5 = Severe Problem

Reflux Finding Score (RFS)

Subglottic edema (SE)	0 = absent; 2 = present
Ventricular (V)	2 = partial; 4 = complete
Erythema/hyperemia (E.H)	2 = arytenoids only; 4 = diffuse
Vocal fold edema (VFE)	1 = mild; 2 = moderate; 3 = severe; 4 = polypoid
Diffuse laryngeal edema (DLE)	1 = mild; 2 = moderate; 3 = severe; 4 = obstructing
Posterior commissure hypertrophy (PCH)	1 = mild; 2 = moderate; 3 = severe; 4 = obstructing
Granuloma/granulation tissue (G.GT)	0 = absent; 2 = present
Thick endolaryngeal mucus (TEM)	0 = absent; 2 = present

Data

Time: 2012 ~ 2016

Number of patients: 74

- All patients received PPIs (40mg/day) treatment for 2 months

Variables

- Age
- Sex
- BMI (1 missing value)
- RSI pretest
- RSI posttest
- Doctor 1, 2 RFS pretest
- Doctor 1, 2 RFS posttest (4 missing values)

Method

Comparing pretest and posttest	Comparing RFS between 2 doctors	Comparing RFS and RSI	Analyzing variables affecting treatment response
• Descriptive statistics • t-test • Visualization	• Scatter plot • Correlation coefficient • ICC • Bland-Altman plot • t-test	• Scatter plot • Correlation coefficient	• Descriptive statistics • t-test • Correlation coefficient • Linear regression

Result & Discussion

Comparing pretest and posttest

	Mean (SD)				Sample size (Percentage)				Differences (95% C.I.)	p-value
	Pretest		Posttest		Pretest		Posttest			
RSI	19.22	(5.18)	8.99	(5.69)	74		74		10.23 (8.62, 11.84)	< .001
Normal (<13)	12	(0)	6.41	(3.24)	1	(1.35%)	56	(75.68%)		
Abnormal (≥13)	19.32	(5.15)	17	(3.91)	73	(98.65%)	18	(24.32%)		
RFS_rater1	7.9	(2.44)	6.71	(2.14)	70*		70*		1.19 (0.82, 1.55)	< .001
Normal (<7)	4.38	(1.15)	4.4	(1.04)	16	(22.86%)	25	(35.71%)		
Abnormal (≥7)	8.94	(1.58)	8	(1.37)	54	(77.14%)	45	(62.29%)		
RFS_rater2	6.33	(1.83)	5.74	(1.63)	70*		70*		0.59 (0.19, 0.98)	.005
Normal (<7)	4.77	(0.65)	4.68	(0.74)	35	(50%)	44	(62.86%)		
Abnormal (≥7)	8.11	(1.18)	7.54	(1.03)	35	(50%)	26	(37.14%)		

*: Samples included after deleting 4 missing values

Table 1. Descriptive statistics and t-test of pretest and posttest of RSI and RFS
The differences between mean RSI and mean RFS total scores of pretest and posttest were analyzed by t-test. Table 1 shows that the mean RSI pretest total score and mean RFS pretest total score are statistically significantly higher than the posttest. The number of normal cases in the posttest is higher than that in the pretest. The number of abnormal cases in the RSI posttest has dropped significantly (24.32%), while the RFS has no significant difference.
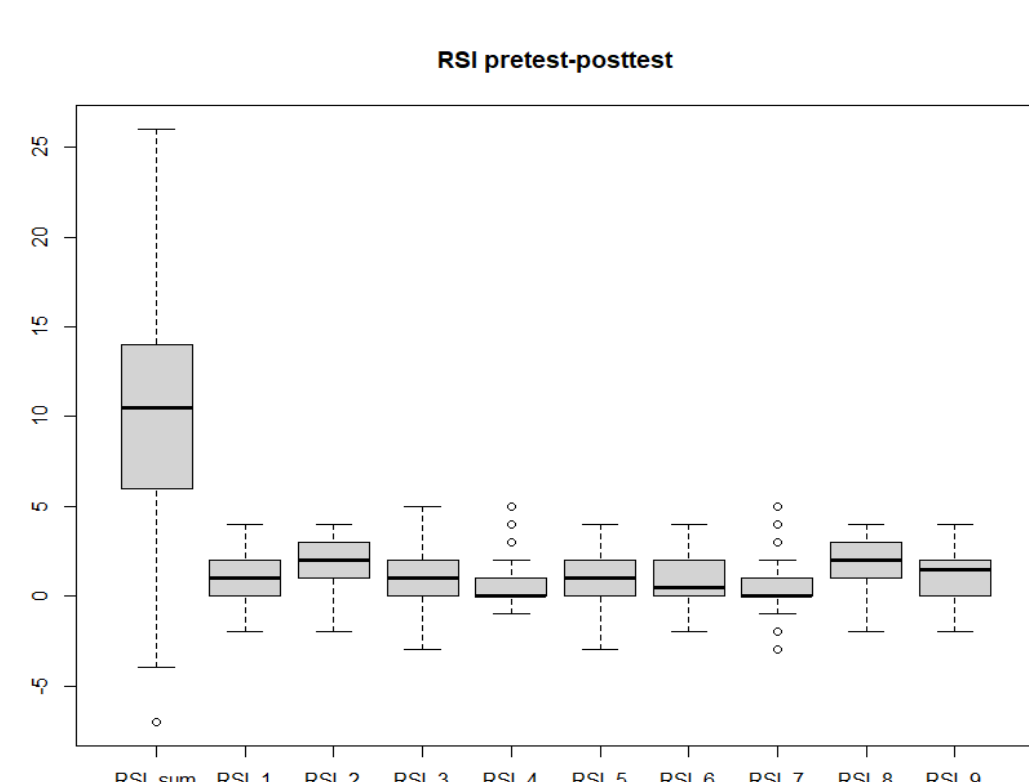

Figure 1. Boxplot of RSI change
The mean difference between pretest and posttest of RSI total score of is 10.23 (SD=6.94). Figure 1 shows the change of RSI total score and 9 indicators.

	t-test			Paired t-test	
	Pretest mean	Posttest mean	p-value	Mean of differences	p-value
RSI_1	2.58	1.35	<.001	1.23	<.001
RSI_2	3.28	1.58	<.001	1.70	<.001
RSI_3	2.54	1.51	<.001	1.03	<.001
RSI_4	1.24	0.64	.002	0.61	<.001
RSI_5	1.50	0.55	<.001	0.95	<.001
RSI_6	1.31	0.50	<.001	0.85	<.001
RSI_7	1.32	0.61	<.001	0.72	<.001
RSI_8	3.32	1.53	<.001	1.80	<.001
RSI_9	2.11	0.76	<.001	1.35	<.001

Table 2. T-test and paired t-test of pretest and posttest for 9 indicators of RSI
The mean score of each indicator of the RSI pretest is statistically significantly higher than the posttest.
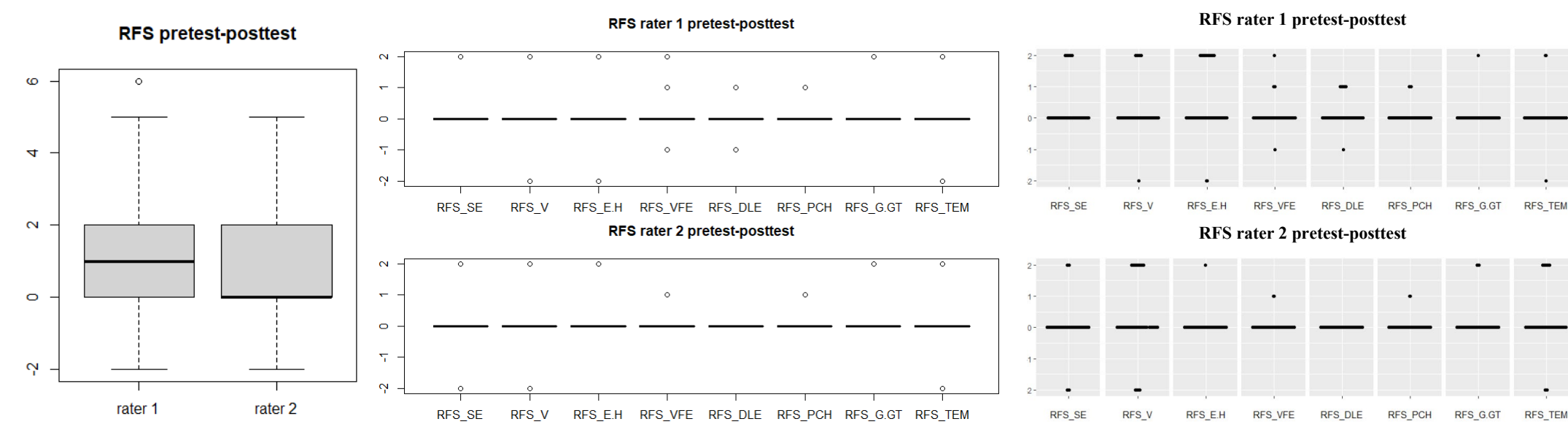

Figure 2. Boxplot of RFS change

Figure 3. Beeswarm plot of RFS change

The mean difference of the RFS total score rated by doctor 1 and doctor 2 is 1.53 (SD = 2.09) and 0.82 (SD = 1.94), respectively. Figure 3 shows its distribution frequency.

	Doctor 1					Doctor 2				
		t-test		Paired t-test			t-test		Paired t-test	
	Pretest mean	Posttest mean	p-value	Mean differences	p-value	Pretest mean	Posttest mean	p-value	Mean differences	p-value
RFS_SE	1.27	0.94	**.049**	0.29	**.001**	0.70	0.71	.943	0	1
RFS_V	1.70	1.51	.193	0.2	**.019**	1.73	1.54	.321	0.2	.128
RFS_E.H	1.22	0.80	**.038**	0.43	**<.001**	0.03	0.00	.321	0.03	.321
RFS_VFE	1.09	1.04	.265	0.06	.159	1.05	1.01	.189	0.04	.083
RFS_DLE	1.24	1.16	.217	0.1	**.019**	1	1	NA	0	NA
RFS_PCH	1.11	1.06	.268	0.06	**.045**	1.04	1.01	.335	0.03	.159
RFS_G.GT	0.14	0.11	.798	0.03	.321	0.30	0.17	.242	0.14	**.024**
RFS_TEM	0.11	0.09	.756	0.03	.567	0.41	0.29	.345	0.14	.167

Table 3. T-test and paired t-test of pretest and posttest for 8 indicators of RFS

> There are statistically significant differences between the pretest and posttest of either RFS or RSI, indicating that PPI treatment is effective for LPRD.
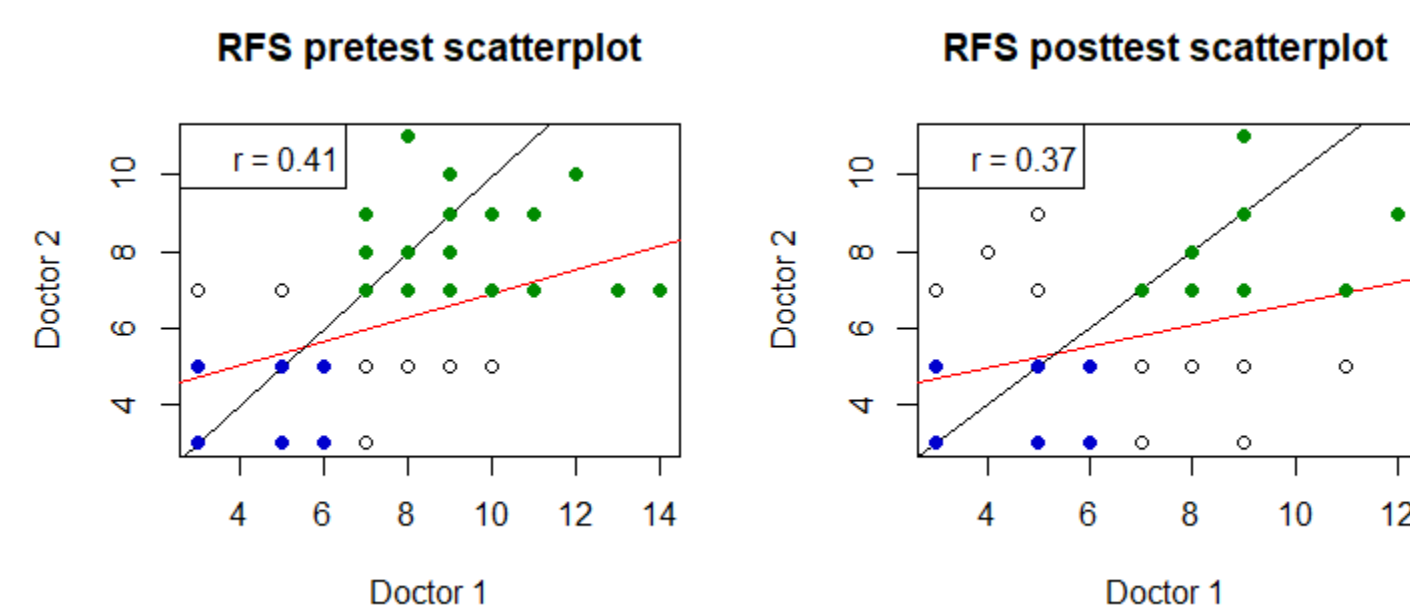
Comparing RFS between 2 doctors

Figure 4. Scatterplot of RFS doctor 1 vs 2
In figure 4, the green dots are the cases both rated as abnormal by two doctors, and the blue dots are the cases both rated as normal.

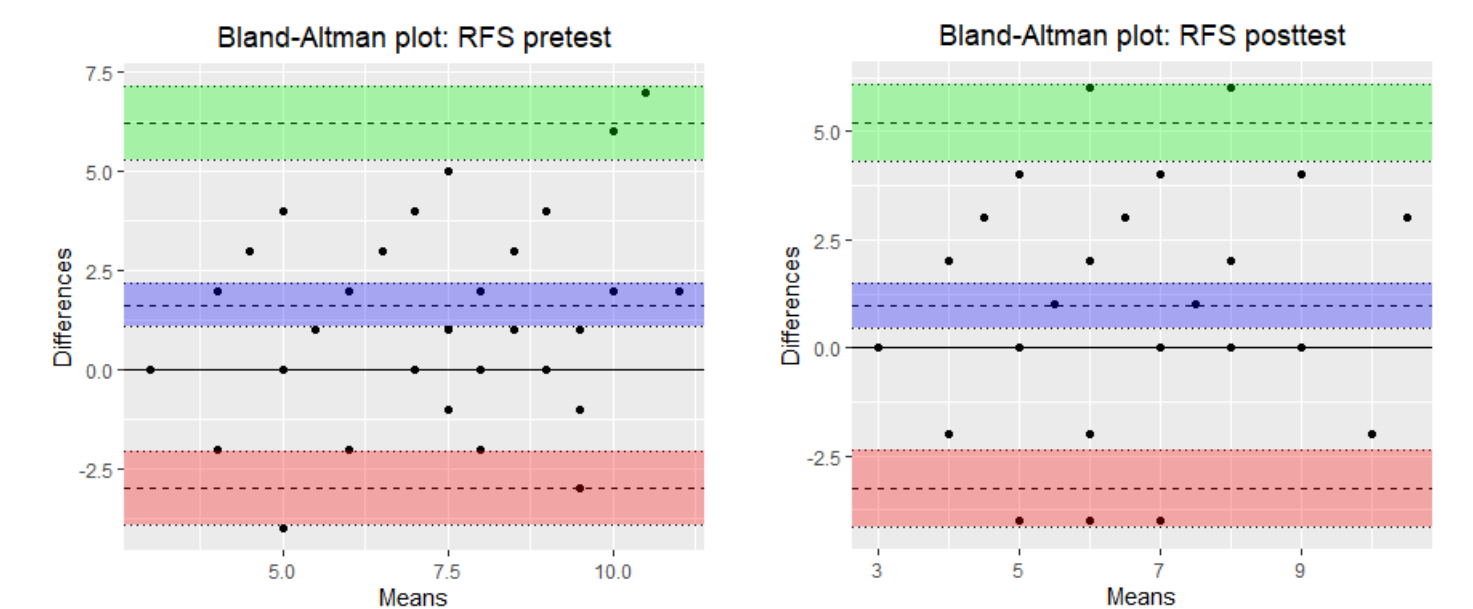|	Correlation coefficient (95% C.I.)	ICC (95% C.I.)
Pretest	0.41 (0.19, 0.58)	0.22 (0.00, 0.43)
Posttest	0.37 (0.15, 0.56)	0.28 (0.05, 0.48)

Figure 5. Bland-Altman plot of RFS doctor 1 vs 2
There is no obvious bias of the rating.

	Mean difference	95% C.I.	P-value
Pretest	1.62	1.07, 2.16	< .001
Posttest	0.97	0.46, 1.49	< .001
change	0.6	0.15, 1.05	**.009**

Table 4. Paired t-test of RFS between 2 doctors

	RFS change (pretest-protest)		pretest		posttest	
	Mean differences (95% C.I.)	p-value	Mean differences (95% C.I.)	p-value	Mean differences (95% C.I.)	p-value
RFS_SE	0.29 (0.05, 0.52)	.017	0.57 (0.31, 0.83)	**<.001**	0.23 (-0.04, 0.49)	.088
RFS_V	0 (-0.24, 0.24)	1	-0.03 (-0.28, 0.22)	.829	-0.03 (-0.28, 0.22)	.82
RFS_E.H	0.4 (0.16, 0.64)	**.001**	1.19 (0.90, 1.48)	**<.001**	0.8 (0.53, 1.07)	**<.001**
RFS_VFE	0.01 (-0.06, 0.09)	.708	0.04 (0.03, 0.11)	.260	0.03 (-0.01, 0.07)	.159
RFS_DLE	0.1 (0.02, 0.18)	.019	0.24 (0.14, 0.35)	**<.001**	0.16 (0.07, 0.24)	**<.001**
RFS_PCH	0.03 (-0.03, 0.09)	.321	0.07 (-0.00, 0.14)	.058	0.04 (-0.01, 0.09)	.083
RFS_G.GT	-0.11 (-0.23, -0.00)	.045	-0.16 (-0.31, -0.01)	.033	-0.06 (-0.17, 0.06)	.321
RFS_TEM	-0.11 (-0.31, 0.08)	.251	-0.33 (-0.46, -.13)	**<.001**	-0.2 (-0.37, -0.03)	.019

Table 5. T-test and paired t-test of 2 doctors for 8 indicators of RFS

> The RFS between doctors are statistically significantly different.
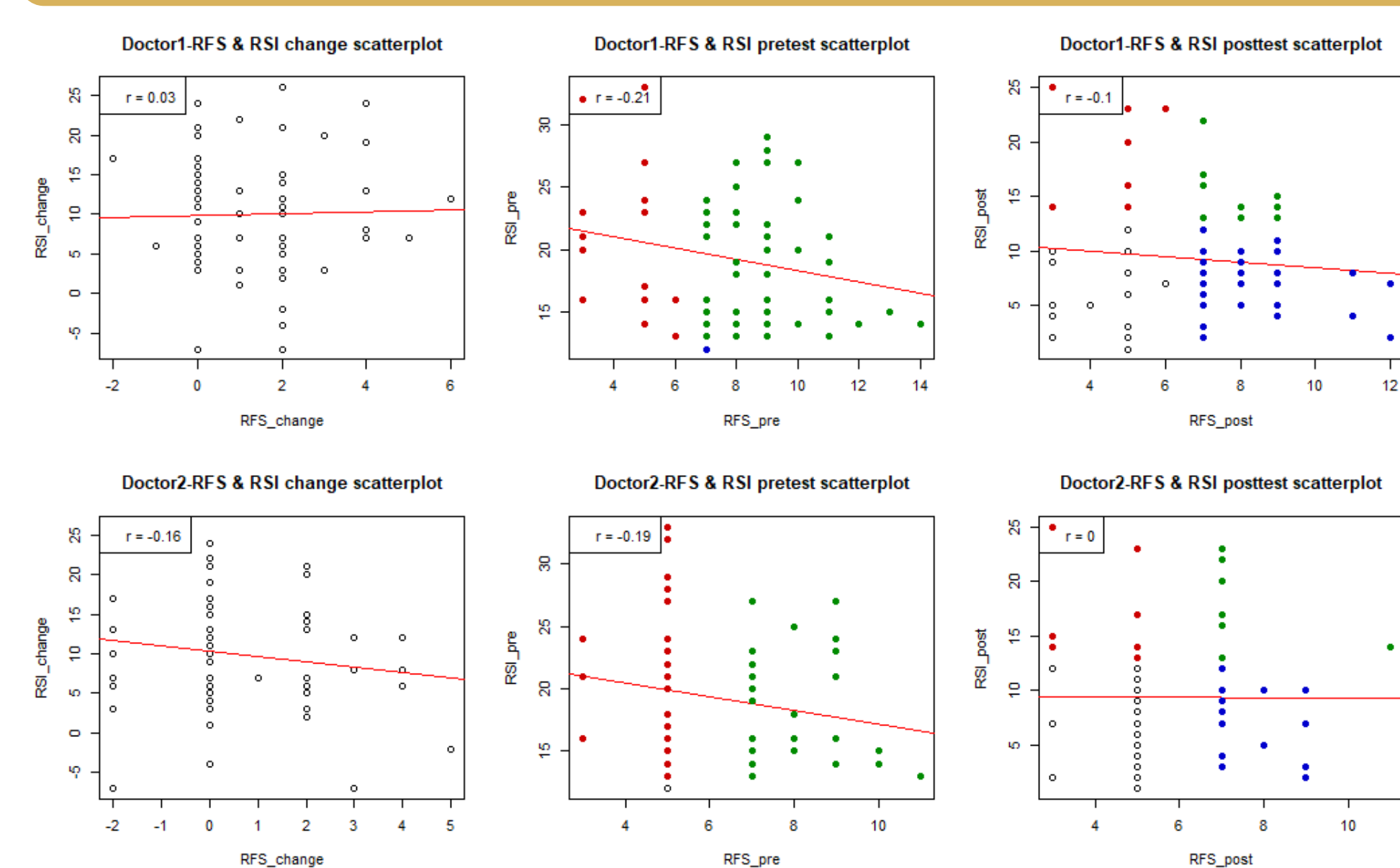
Comparing RFS and RSI

Figure 6. Scatterplot of RFS vs RSI
Figure 6 shows the correlations of the total score of RFS and RSI are low. The green dots are cases RSI ≥ 13 and RFS ≥ 7, which are both labeled as abnormal. The red dots are cases only RSI ≥ 13. The blue dots are cases only RFS ≥ 7. The white dots are cases RSI < 13 and RFS < 7, which are both labeled as normal.

> RFS and RSI have low to no correlation.

Analyzing variables affecting treatment response

Since the ICC of two doctors' RFS is not good, RFS is not suitable for clinical evaluation. Therefore, only RSI is selected to evaluate the PPI treatment response. And the response variable is the percentage change of RSI:

$$RSI\ Percentage\ change = \frac{RSI_{pre} - RSI_{post}}{RSI_{pre}}$$

The mean RSI percentage change is 0.51 (SD=0.32). 73 samples which have complete RSI pretest, posttest, sex, BMI, age data are included in the following analysis.
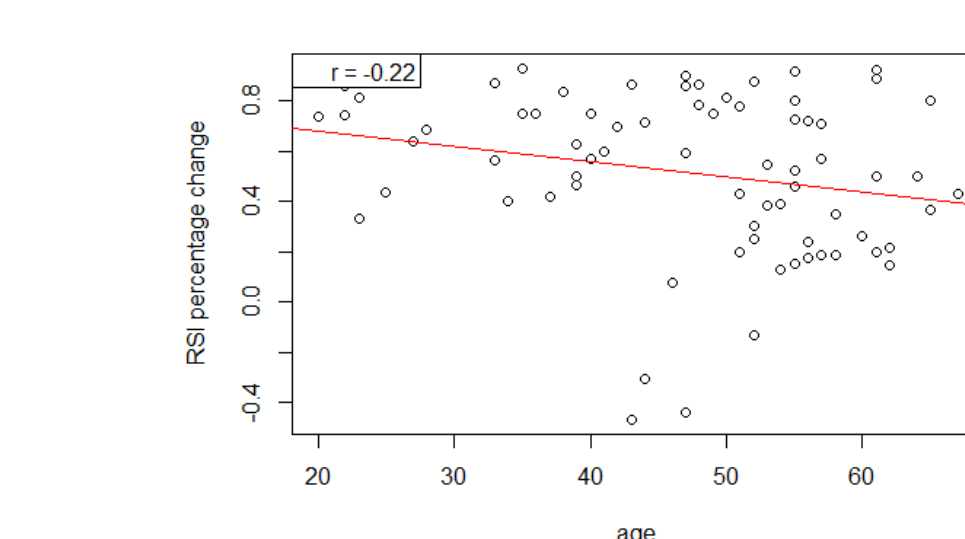

Figure 9. Scatterplot of age vs RSI percentage change
The mean age is 47 years old (SD=11.84). The correlation coefficient of age and RSI percentage change is -0.22 (95% C.I.: -0.43, 0.00). Linear regression equation:

$$RSI\ percentage\ change = 0.8 - 0.006 * age$$

The p-value of the age term is 0.05. Adjusted R-squared is 3.7%. The RSI percentage change decreases 0.6% averagely for each year of age increase.
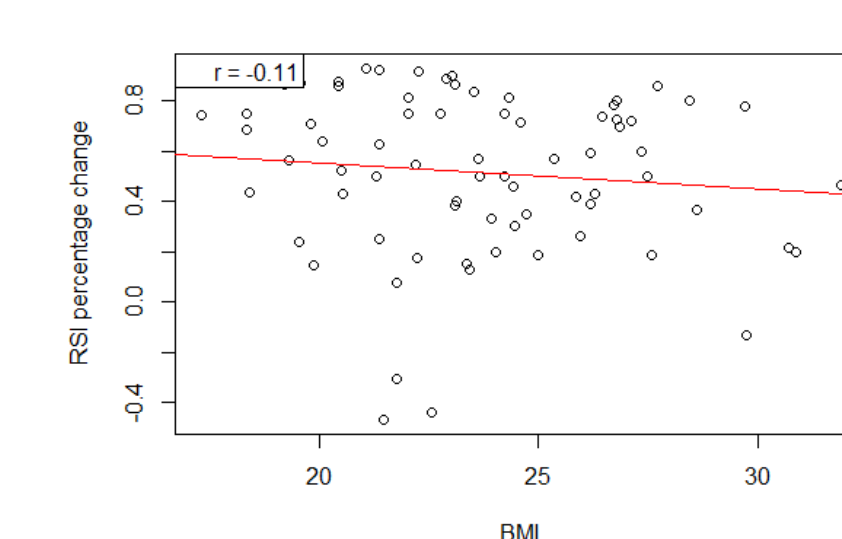

Figure 8. Scatterplot of age vs RSI percentage change
The mean BMI is 23.74 (SD=3.29). The correlation coefficient of BMI and RSI percentage change is -0.11 (95% C.I.: -0.33, 0.13).
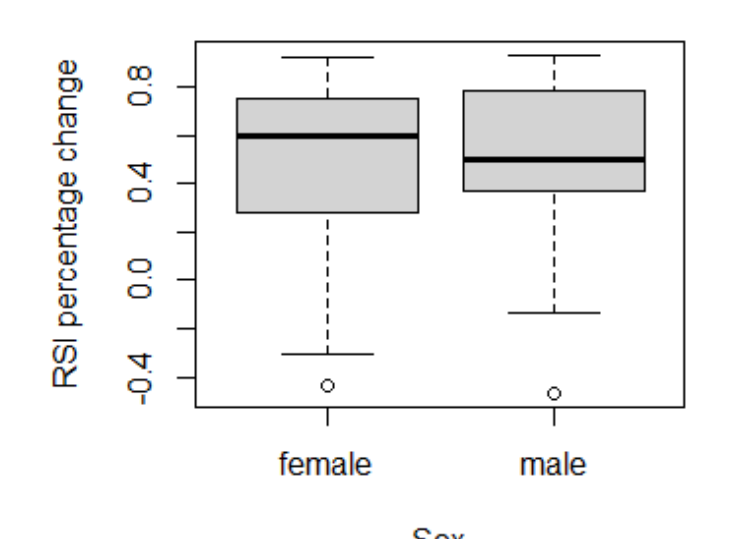

Figure 7. Boxplot of RSI percentage change of female & male
The sample includes 48 females and 25 males. The mean RSI percentage change of female is 0.53 (SD=0.31); male is 0.49 (SD=0.33). The p-value in t-test is 0.62, the RSI percentage change between female and male is not statistically significantly different.

> The older the age, the less the RSI percentage change, that is, the worse treatment response is.