中文題目：**Rosiglitazone 對於糖尿病前期之冠心症病人在降低發炎指標與次級預防心血管疾病的角色**

英文題目：**Anti-inflammatory Effect of Rosiglitazone Treatment on Secondary Prevention of Cardiovascular Events Among Subjects with Pre-diabetes and Coronary Artery Disease**

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Background

Microvascular and macrovascular complications are common in type 2 diabetes mellitus (DM). Thiazolidinedione (TZD), a synthetic activator of PPARγ, is not only an insulin sensitizer but also an activator in adipose transcriptional regulation and anti-inflammatory process. Though accumulated scientific evidence supports the anti-inflammatory effects on DM subjects, it remains unclear whether TZD can provide similar effects on pre-DM with documented coronary artery disease (CAD).

Materials and Methods

We performed a randomized, double blind, placebo-controlled study to examine whether TZD can have beneficial effects on inflammatory and insulin sensitivity biomarkers among adults with pre-DM with angiographic documented CAD. Among total 105 patients with CAD, 46 of them had pre-diabetes and were randomly assigned to receive pioglitazone 4mg (TZD group, n=23) or dummying placebo (placebo group, n=23). The median follow-up period was 2 years. Biomarkers were taken before the trial and 6 months later, respectively. Regarding insulin resistance, resistin and adiponectin were measured; chemokine ligand/monocyte chemotactic protein-1 (CCL/MCP1), secretary phospholipases A_2 ($sPLA_2$) and high-sensitivity C-reactive protein (hsCRP) were analyzed for inflammation status changes. The primary end-point was defined as the diagnosis of diabetes mellitus or major cardiovascular events, including myocardial infarction, overt heart failure, and surgery or coronary intervention for CAD.

Results

The mean age was 66.8±0.5 years, and 84% were men with similar baseline

characteristic profile including age, gender, family history, body weight, and disease severity between the TZD and placebo groups. In the TZD group, insulin sensitivity profile improved significantly with decreased resistin (before vs. after: 3.56±2.16 vs. 2.83±1.92 ng/ml, Δ=-20.6%, $p<0.05$) and increased adiponectin (before vs. after: 5858±3139 vs. 20552±15980 ng/ml, Δ=+250%, $p<0.01$), which remained similar for placebo group (resistin: before vs. after: 2.33±1.89 vs. 2.18±1.56 ng/ml; adiponectin: before vs. after: 4773±2103 vs. 5372±2595 ng/ml, both $p>0.05$; respectively). Regarding inflammatory profiles, most markers including CCL/MCP1 (before vs. after: 357.7±85.8 vs. 295.3±41.4 pg/ml, Δ=-17.4%) and hsCRP (before vs. after: 3508±0.597 vs. 1671±0.597 ng/ml, Δ=-49.3%) (both $p<0.05$).

However, some paradoxical changes regarding our hypothesis were not observed on several pro-inflammatory markers, including sCD40 ligand (before vs. after: 3913±3635 vs. 7138±6108 pg/ml) and $sPLA_2$ (before vs. after: 2114±899 vs. 2615±1511 pg/ml) (both $p<0.05$). Those paradoxical phenomenons deserved further investigation to elucidate the possible mechanisms during TZD treatment. In the major cardiovascular events, one patient was observed with progression to DM, one had AMI event with heart failure, one received bypass surgery and another patient received additional coronary intervention procedure. All these major cardiovascular outcome happened significantly greater among placebo group, but none in the TZD group (palcebo vs. TZD group: 17.3% (4/23) vs. 0% (0/23), $p=0.038$ by Log-Rank test for Kaplan-Mier survival analysis).

Conclusion

For the first time, we successfully demonstrated that long-term use of TZD could reduce the insulin resistance and major cardiovascular events, as well as novel inflammatory biomarkers, including CCL/MCP1 and hsCRP among those with pre-diabetes with documented CAD. These observational results may imply the role of TZD in the secondary prevention of cardiovascular events at an earlier stage, which is currently not the indication for TZD therapy.

表一 (Table 1)

factor	安慰劑 （n＝12）	TZD （n＝14）	P value
年齡（years）	63±9.62	70.14±9	0.062
體重（kg）	72.67±9.53	66.64±6.11	0.063
心導管（個）	2.42±0.79	2.04±0.83	0.291
高血壓（％）	83	93	0.58
充血性心衰竭（％）	0	0	N/A
高血脂（％）	67	50	0.453
中風（％）	0	0	N/A
抽菸（％）	67	36	0.238
慢性腎臟病（％）	0	7	1
心肌梗塞（oldMI）	25	21	1
冠狀動脈繞道手術（％）	0	7	1
家族病史（％）	0	0	N/A
性別（％）	男：92	男：79	0.598

1. 數值表示若為常態分佈：平均值±標準差。若為類別：百分比。

2. 類別變項資料以卡方檢定。

數值型資料因為是常態分布，故以獨立 T 檢定 (independent T test)分析。

* p <0.05；**p<0.01。

3. N/A 表無法進行檢定分析，因為有一個類別均為零，但某個類別皆為零其實就代表這個 factor 無任何影響力。

4. 括號內為單位

表二(Table 2)

variation		治療前	治療後	P value
Resistin	安慰劑（ng/ml）	2.33±1.89	2.18±1.56	0.688
	TZD（ng/ml）	3.56±2.16	2.83±1.92	0.027*
Adiponectin	安慰劑（ng/ml）	4773±2103	5372±2595	0.175
	TZD（ng/ml）	5858±3139	20552±15980	0.002**
RBP-4	安慰劑（ng/ml）	1394±183	1469±309	0.369
	TZD（ng/ml）	1495±265	1455±200	0.488
MPO	安慰劑（ng/ml）	72.34±24.24	97.94±115.36	0.462
	TZD（ng/ml）	94.60±48.68	63.02±27.16	0.043*
MIF	安慰劑（ng/ml）	32.15±11.01	26.83±7.93	0.095
	TZD（ng/ml）	28.72±8.89	25.73±7.22	0.467
sCD40 ligand	安慰劑（pg/ml）	5680±3623	9163±5752	0.177
	TZD（pg/ml）	3913±3635	7138±6108	0.168
CCL/MCP1	安慰劑（pg/ml）	349.7±114.4	343.3±122.0	0.767

	TZD（pg/ml）	357.7±85.8	295.3±41.4	0.014*
sPLA2	安慰劑（pg/ml）	2252±988	1764±947	0.091
	TZD（pg/ml）	2114±899	2615±1511	0.283
hsCRP*	安慰劑（ng/ml）	2672±0.637	2781±0.637	0.583
	TZD（ng/ml）	3508±0.597	1671±0.597	0.035*

1.數值表示若為常態分布：平均值±標準差

若非常態分布〈在variation有*〉：中位數±標準誤

2.數值型資料若為常態分布則以配對T檢定分析（pair T test），若分非常態分布則以無母數中位數檢定分析（Wilcoxon test），* p <0.05；**p<0.01；***p<0.001

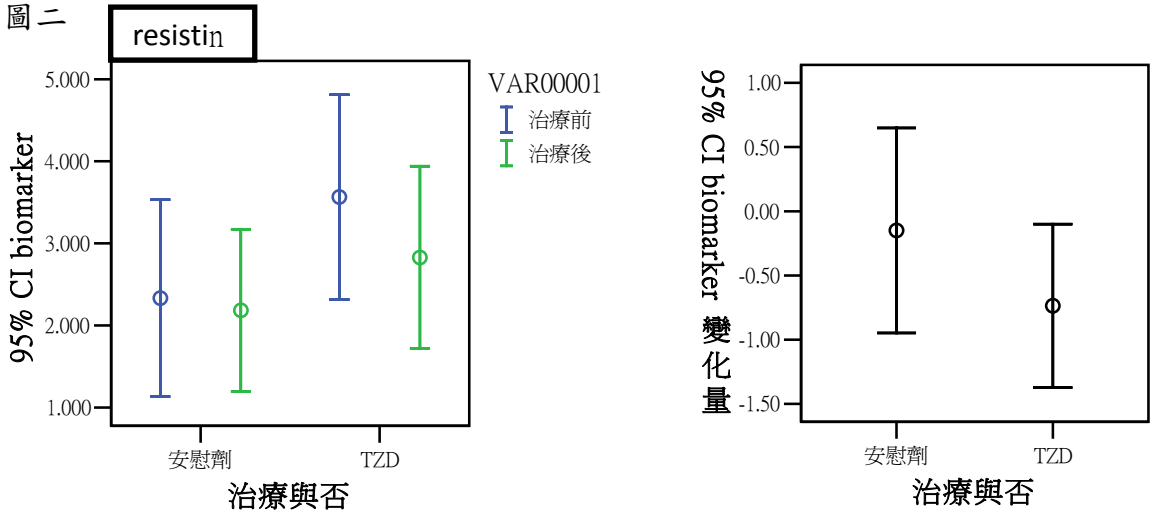
3.括號內為單位

一. 胰島素抗性

1. resistin：安慰劑：治療前＝2.33±1.89　治療後＝2.18±1.56 ng/ml　P＞0.05

TZD：　治療前＝3.56±2.16　治療後＝2.83±1.92 ng/ml　P＜0.05

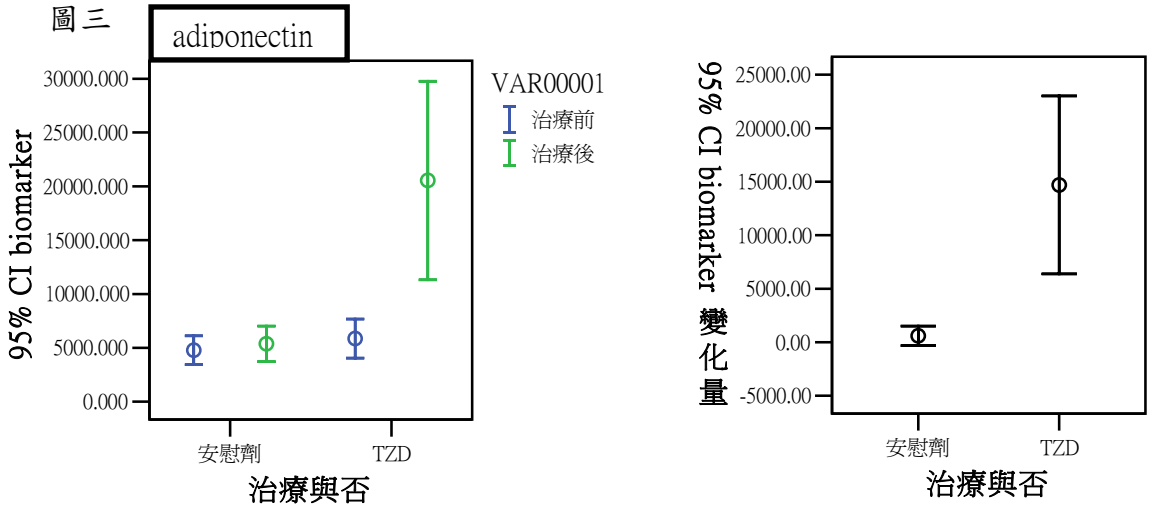
圖二



2. adiponectin：安慰劑：治療前＝4773±2103　治療後＝5372±2595 ng/ml　P＞0.05

TZD：　治療前＝5858±3139　治療後＝20552±15980 ng/ml　P＜0.01

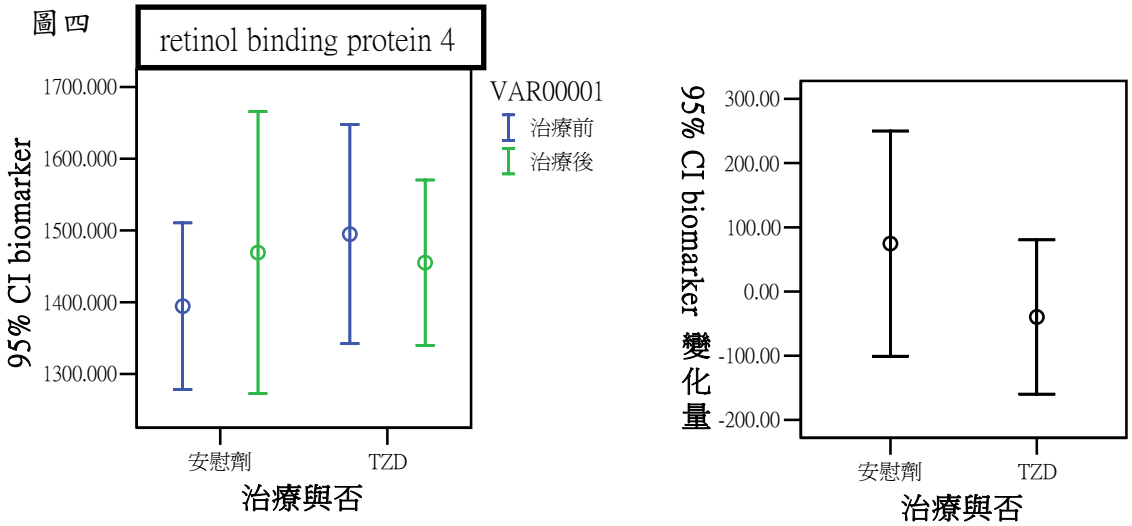
圖三



3. RBP-4：安慰劑：治療前＝1394±183　治療後＝1469±309 ng/ml　P＞0.05

TZD：　治療前＝1495±265　治療後＝1455±200 ng/ml　P＞0.05

圖四

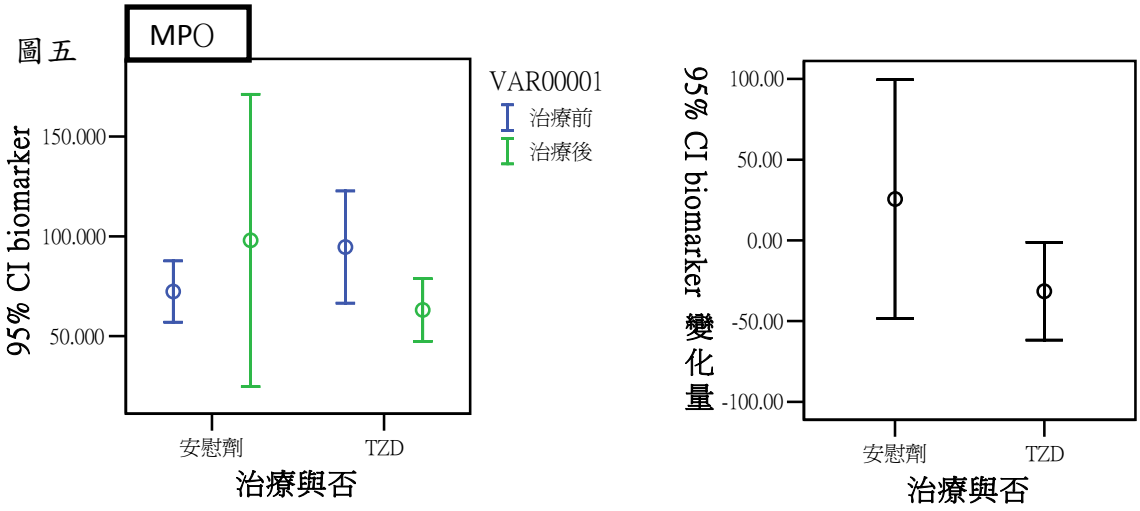


二. 抗氧化及發炎反應（包含吸引單核球）

1. MPO：安慰劑：治療前＝72.34±24.24　治療後＝97.94±115.36 ng/ml　P＞0.05

TZD：　治療前＝94.60±48.68　治療後＝63.02±27.16 ng/ml　P＜0.05

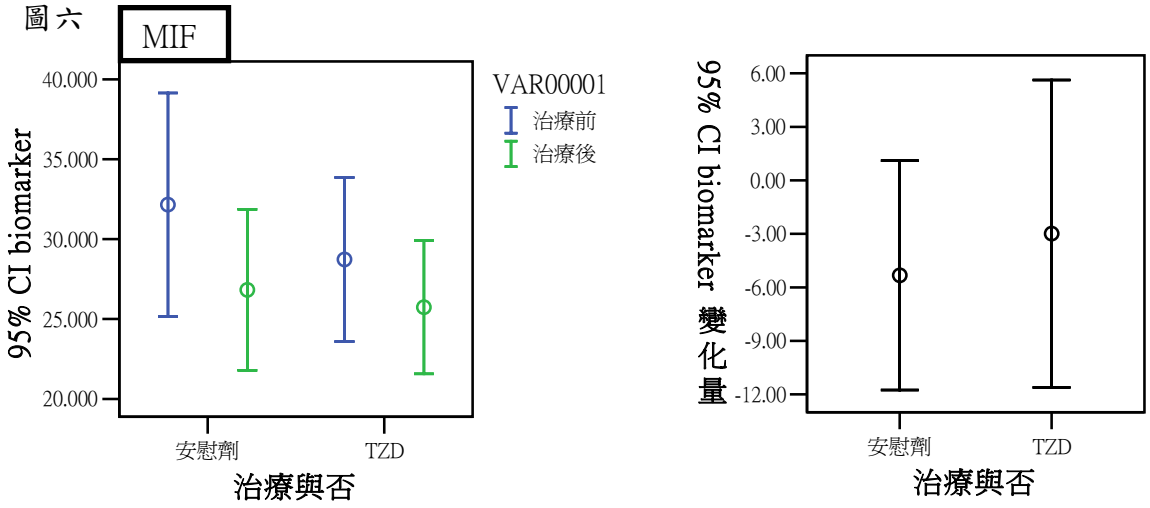
圖五



2. MIF：安慰劑：治療前＝32.15±11.01　治療後＝26.83±7.93 ng/ml　P＞0.05

TZD：　治療前＝28.72±8.89　治療後＝25.73±7.22 ng/ml　P＞0.05

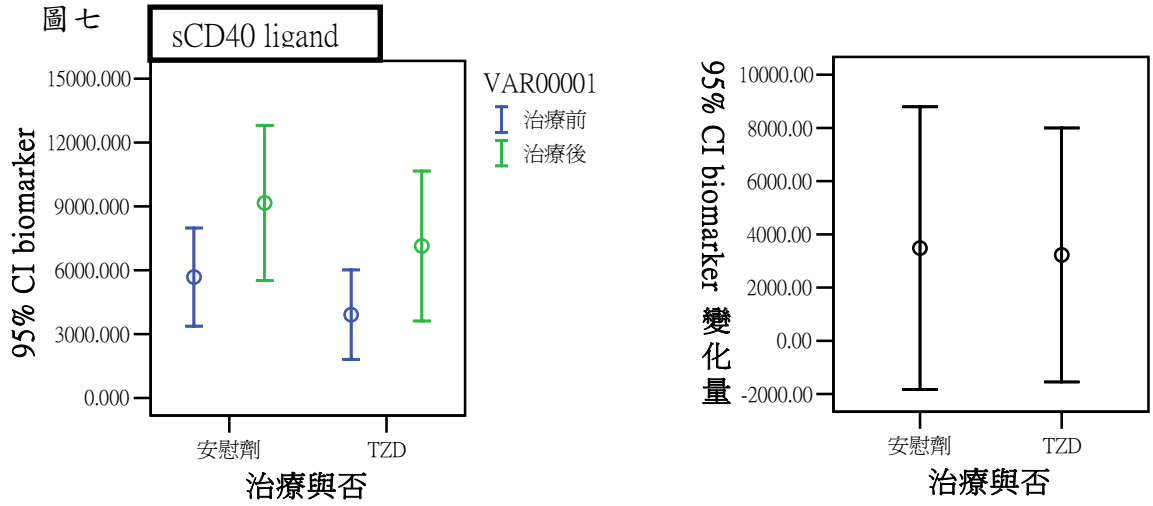
圖六



3. sCD40 ligand：安慰劑：治療前＝5680±3623　治療後＝9163±5752 pg/ml　P＞0.05

TZD：　治療前＝3913±3635　治療後＝7138±6108 pg/ml　P＞0.05

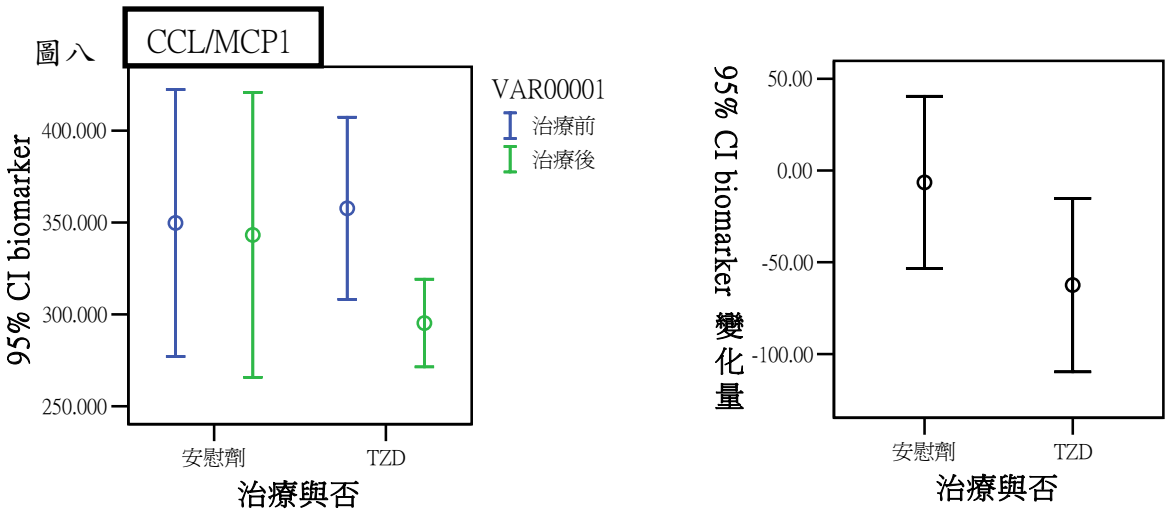
圖七



4. CCL/MCP1：安慰劑：治療前＝349.7±114.4 治療後＝343.3±122.0 pg/ml P＞0.05

TZD： 治療前＝357.7±85.8 治療後＝295.3±41.4 pg/ml P＜0.05

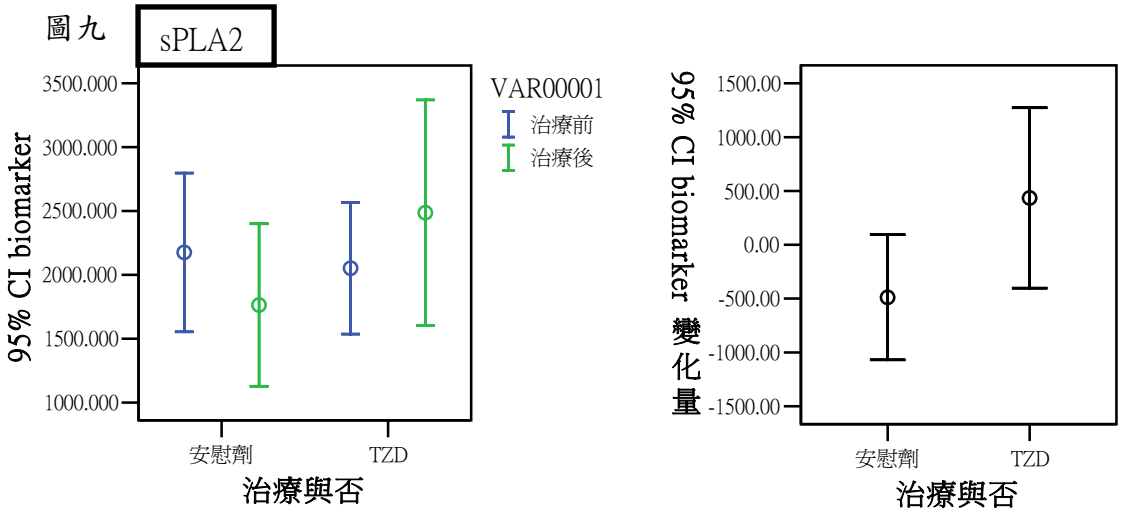
圖八



5. sPLA2：安慰劑：治療前＝2252±988 治療後＝1764±947 pg/ml P＞0.05

TZD： 治療前＝2114±899 治療後＝2615±1511 pg/ml P＞0.05

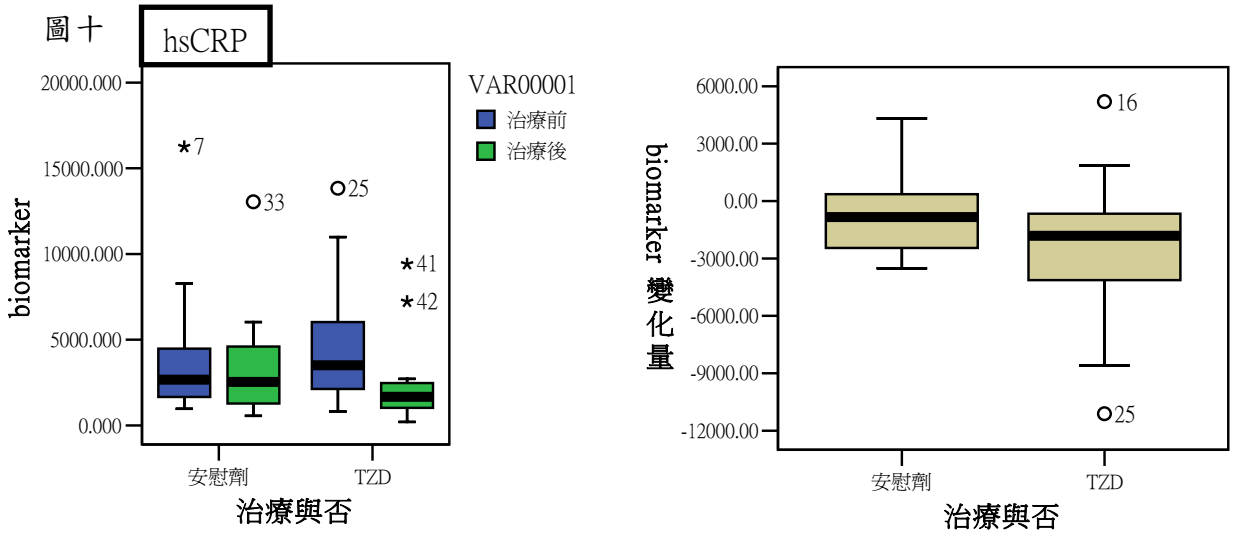
圖九



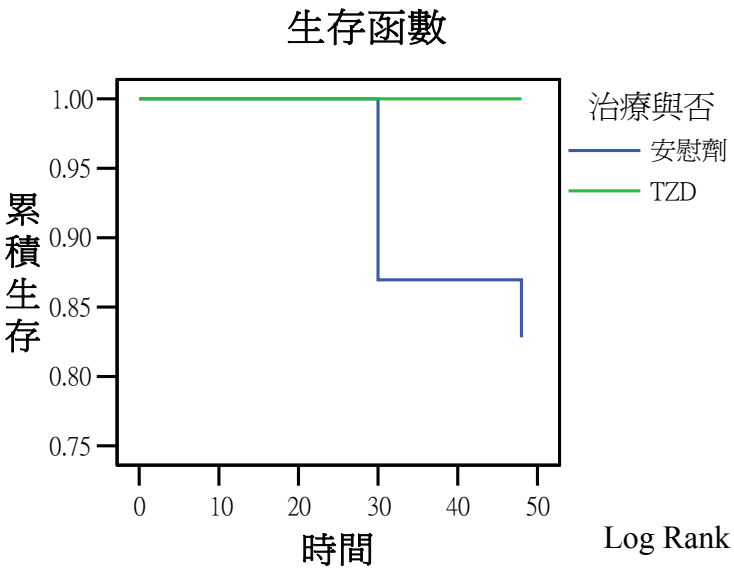
6. hsCRP：安慰劑：治療前＝2672±0.637 治療後＝2781±0.637 ng/ml P＞0.05

TZD： 治療前＝3508±0.597 治療後＝1671±0.597 ng/ml P＜0.05

圖十



圖十一



Log Rank Test

P-value = 0.0384*