



# Incremental Value of Serial Preablative Thyroglobulin Measurements in Identifying Distant Metastatic Differentiated Thyroid Cancer



Teng Zhao<sup>1</sup>, Tianjun Li<sup>2</sup>, Ke Yang<sup>1</sup>, Jun Liang<sup>2#</sup>, Yansong Lin<sup>1#</sup>  
<sup>1</sup>Department of Nuclear Medicine, Peking Union Medical College Hospital, Beijing, China  
<sup>2</sup>Department of Oncology, the Affiliated Hospital of Qingdao University, Qingdao, China

## Objectives

Serum thyroglobulin (Tg) is a well-established tumor marker in the follow-up of patients with differentiated thyroid carcinoma (DTC) after thyroidectomy combined with radioiodine (RAI) ablation. As to pre-RAI stimulated thyroglobulin (PR-sTg), though several studies have manifested its potential in identifying distant metastatic DTC (DM-DTC), it remains unclear whether a single PR-sTg is sufficient for predicting DM-DTC. This retrospective study was aimed to evaluate the utility of serial PR-sTg measurements in identifying DM-DTC.

## Methods

A series of PR-sTg, thyroid-stimulating hormone (TSH) and anti-Tg antibody (TgAb) was measured in 317 consecutive DTC patients before RAI administration, among which data collected at the first time were marked as Tg1, TSH1 and TgAb1, respectively, while as Tg2, TSH2 and TgAb2 at the last time. Patients were divided into 2 groups as M1 (n=72) and M0 (n=245) according to the presence of DM or not.

Parameters derived from the change in PR-sTg including  $\Delta Tg$  (Tg2-Tg1),  $\Delta Tg'$  (Tg2/TSH2-Tg1/TSH1) and  $\Delta Tg/\Delta TSH$  ( $\Delta Tg$ /(TSH2-TSH1)) were calculated and further combined with an actual or corrected value of PR-sTg (Tg1, Tg2, Tg1/TSH1 or Tg2/TSH2). All the independent and combined parameters were tested for diagnostic performance in identifying DM-DTC.

## Figures

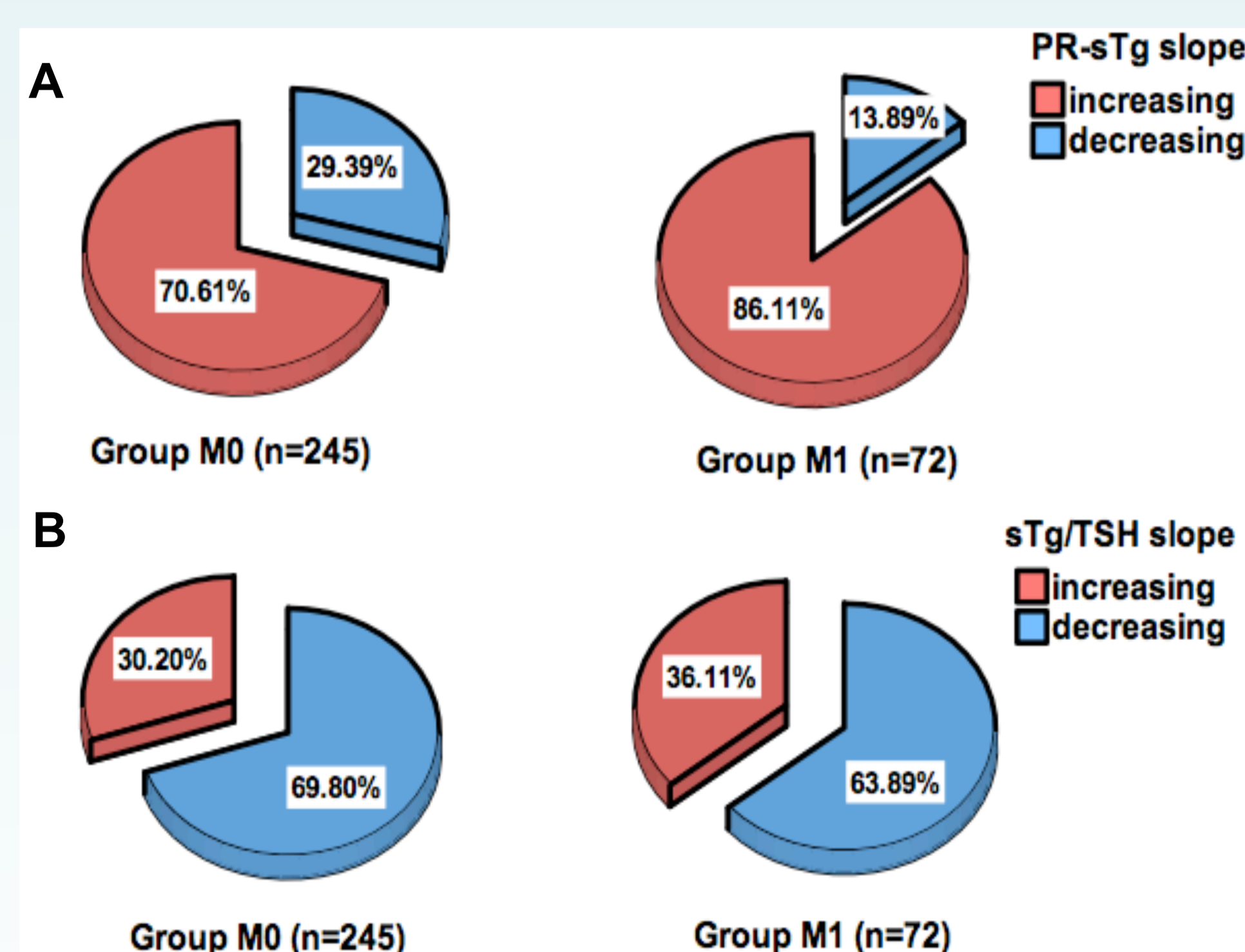


Figure 1 Ratio of patients with different PR-sTg slopes (A) and sTg/TSH slopes (B) in group M0 and group M1.

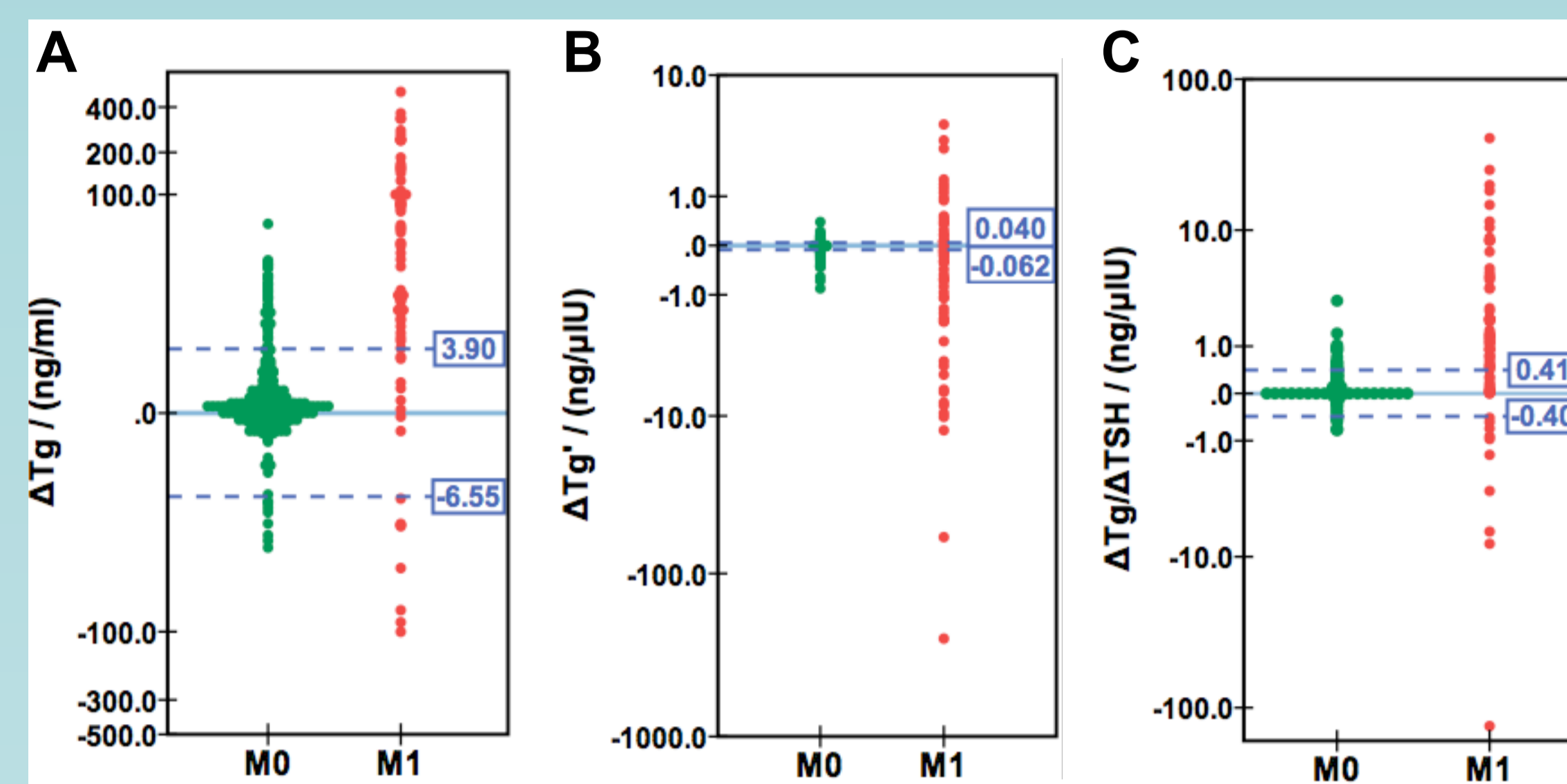


Figure 2 Scatter plot showing the distribution of  $\Delta Tg$  (A),  $\Delta Tg'$  (B) and  $\Delta Tg/\Delta TSH$  (C) in group M0 and group M1. The optimal cut-off values are marked with dotted lines.

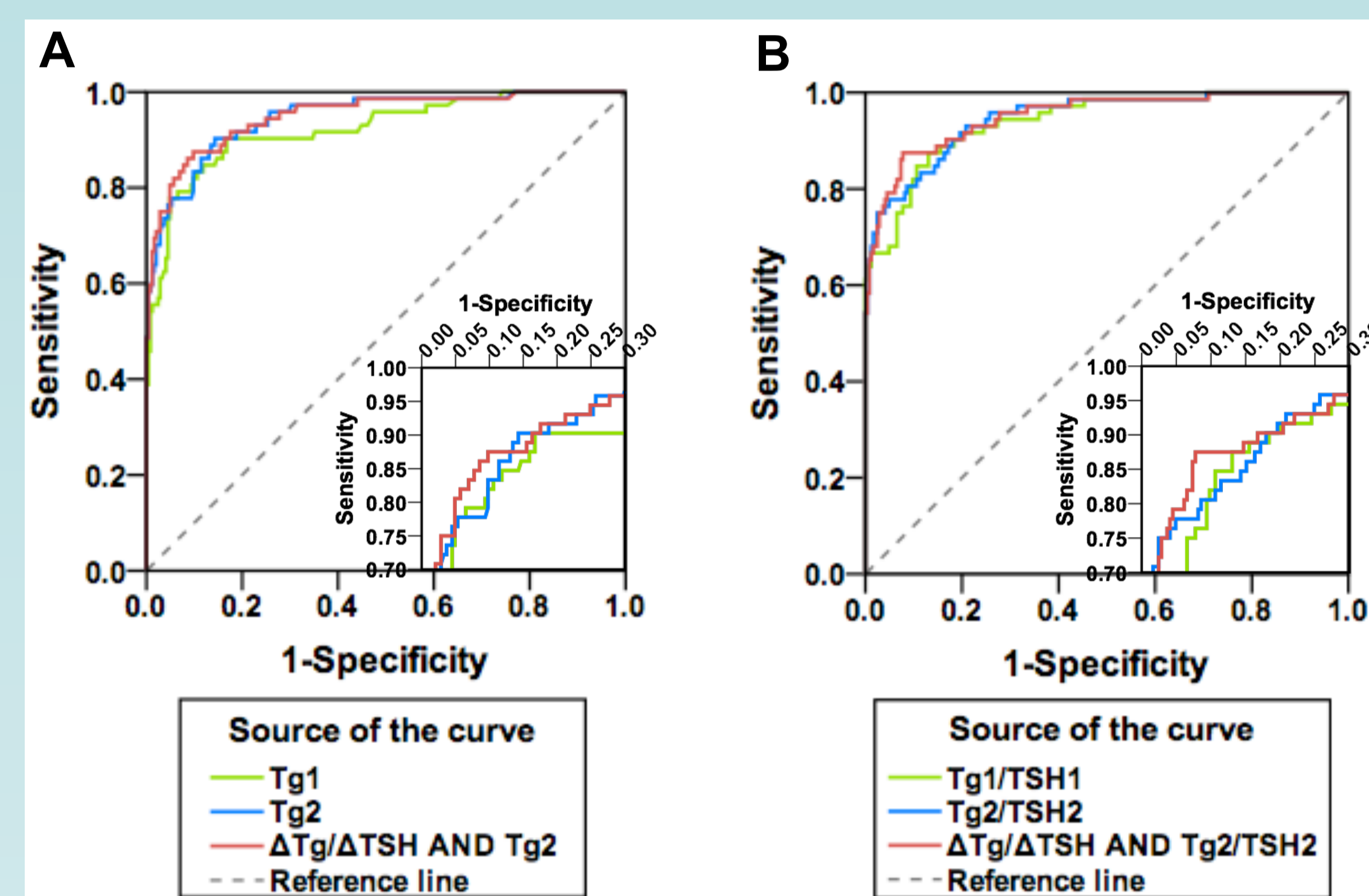


Figure 3 The ROC curves of Tg1, Tg2, the regression model of  $\Delta Tg/\Delta TSH$  combined with Tg2 (A) and Tg1/TSH1, Tg2/TSH2, the regression model of  $\Delta Tg/\Delta TSH$  combined with Tg2/TSH2 (B) for the identification of DM-DTC. Insets: Zoomed views that emphasize the disparities in different ROC curves near the top left corners, which indicate better discrimination abilities for the combined markers.

## Results

The ratio of patients with increasing PR-sTg in M1 was 86.11%, which was higher than 70.61% in M0 ( $\chi^2=6.971$ ;  $P=0.008$ ). While the ratio of patients with different sTg/TSH slopes between the 2 groups was not statistically different ( $\chi^2=0.899$ ;  $P=0.343$ ).

Higher Tg1, Tg2, Tg1/TSH1, Tg2/TSH2 and wider amplitudes of  $\Delta Tg$ ,  $\Delta Tg'$ ,  $\Delta Tg/\Delta TSH$  were observed in M1 (all  $P<0.01$ ).

Tg2 and Tg2/TSH2, with corresponding areas under ROC curves (AUC) of both 0.947, were more accurate than Tg1 and Tg1/TSH1.

$\Delta Tg/\Delta TSH$  manifested the highest accuracy (88.64%) and specificity (90.20%) among the 3 parameters of preablative changes, with a diagnostic range of -0.40~0.41 ng/ $\mu$ IU.

The diagnostic performance was further improved with a larger AUC (0.951) by combining  $\Delta Tg/\Delta TSH$  with Tg2/TSH2.

## Conclusions

Serial PR-sTg measurements may add much incremental value to the identification of DM-DTC.

$\Delta Tg/\Delta TSH$  holds the promise to be a reliable biomarker for DM-DTC.

$\Delta Tg/\Delta TSH$  combined with the sTg/TSH collected immediately before RAI therapy can yield even more favorable diagnostic performance with a decent accuracy and specificity, thus, serial PR-sTg measurements are recommended as a feasible approach to assist in preablative assessment and decision-making.

Correspondence should be addressed to Yansong Lin, Email: linyansong@pumch.cn and Jun Liang, Email: liangjun1959@aliyun.com.

Conflicting interests: Nothing to declare.

Acknowledgements: We gratefully acknowledge the assistance of Prof. Shan Guangliang for guidance in statistical analysis. We thank Mr. Dong Yingsai for his help in English editing and formatting.

Funding Source: This work was supported by the Ministry of Health Industry Special Scientific Research Projects of China (201202012) and National Natural Science Foundation of China (30970850).

Table 3 Diagnostic performance of serological parameters and their pre-RAI changes in identifying DM-DTC.

Parameters	Cut-off value	SN	SP	Accuracy	PPV	NPV
Tg1	12.35 ng/ml	90.28%	83.27%	84.86%	61.32%	96.68%
Tg2	22.10 ng/ml	90.28%	85.71%	86.75%	65.00%	96.77%
Tg1/TSH1	0.287 ng/ $\mu$ IU	87.50%	86.94%	87.07%	66.32%	95.95%
Tg2/TSH2	0.516 ng/ $\mu$ IU	77.78%	95.10%	91.17%	82.35%	93.57%
$\Delta Tg$	-6.55~3.90 ng/ml	88.89%	79.18%	81.39%	55.65%	96.04%
$\Delta Tg'$	-0.062~0.040 ng/ $\mu$ IU	90.28%	84.08%	85.49%	62.50%	96.71%
$\Delta Tg/\Delta TSH$	-0.40~0.41 ng/ $\mu$ IU	83.33%	90.20%	88.64%	71.42%	94.85%
$\Delta Tg/\Delta TSH$ AND Tg2	a AND Tg2 > 73.87ng/ml	87.50%	90.20%	89.59%	72.41%	96.09%
	b AND Tg2 > 8.31ng/ml					
$\Delta Tg/\Delta TSH$ AND Tg2 /TSH2	a AND Tg2/TSH2 > 0.663 ng/ $\mu$ IU	87.50%	92.24%	91.17%	76.83%	96.17%
	b AND Tg2/TSH2 > 0.136 ng/ $\mu$ IU					

Abbreviations: TP, true positive; FP, false positive; TN, true negative; FN, false negative; SN, sensitivity; SP, specificity. a:  $\Delta Tg/\Delta TSH$  is in the range of -0.40~0.41ng/ $\mu$ IU; b:  $\Delta Tg/\Delta TSH$  is out of the range of -0.40~0.41ng/ $\mu$ IU.

