

## Precision and Accuracy of Thyroid Dysfunction Questionnaire (TDQ) for Hyperthyroidism Screening in Childbearing Age Women

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### ABSTRACT

**Background:** Community-based case finding efforts of hyperthyroidism rather not to do, but constrained because *accurate markers* measurements using hormones. TDQ as a screening instrument which meets several criteria diagnostic tests, provide more convenience for the patient, cheaper, easier and simpler. This study aimed to determine the precision and accuracy of diagnostic test of hyperthyroidism screening in childbearing age women.

**Subjects and Method:** The study was a diagnostic study with cross sectional design. It conducted in Prambanan, Sleman, Yogyakarta. The sample consisted of 112 randomly selected of childbearing age women. Clinical symptoms of hyperthyroidism were measured using the TDQ, thyroid status measured by thyroid stimulating hormone (TSH) and free thyroxin (FT4). TDQ diagnostic precision and accuracy were tested using the percent agreement (PA), Kappa coefficient, sensitivity (Se), specificity (Sp), LR (+), LR (-), Youden's index, the area under the curve (AUC) in the receiver operating curve (ROC) and diagnostic odds ratio (DOR).

**Results:** The best value in diagnostic precision is TDQ score with cutoff point score of 40, with PA 81.2 % and Kappa coefficient 0.62. Similarly, the best accuracy value Se 90%, Sp 76%, LR(+) 3.75, LR(-) 0.13, Youden's index 0.66, AUC 0.831 and DOR 28.8.

**Conclusion:** The values and the optimal accuracy obtained from the best score of 40 and this cut off point of the score is sufficient to be used as a threshold determination of a diagnosis of hyperthyroidism by TDQ scores.

**Keywords:** diagnostic tests, *thyroid dysfunction questionnaire* (TDQ), hyperthyroidism, childbearing age women.

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### BACKGROUND

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A region with characteristics that cause a reduction in the iodine content in the soil is referred to as iodine deficiency endemic area (Black, 2003; Djokomoeljanto 2008; Bayram et al., 2009). Prambanan, Sleman is endemic, based on measurements of thyroid goitre rate (TGR) in 2003 was found to be 35.8%. The endemic areas, causing risk of iodine deficiency in all age groups, ranging from fetal, neonatal, children, adolescents, adults and the elderly. The impacts of iodine deficiency include a very wide spectrum,

such as: abortion, stillbirth, congenital defects, perinatal mortality, infant mortality, cretin, goiter, hypothyroidism, decreased IQ, impaired mental function, impaired muscle function, growth retardation and iodine-induced hyperthyroidism or Iih (Dillon and Milliez, 2000; Verma and Raghuvanshi, 2001; Sebotsa et al., 2009).

New problems that occur in areas of endemic iodine deficiency, is the presence of excess iodine, as the impact of the elimination program against iodine deficiency in the form of universal salt iodization (USI)

and supplementation yodiol within a relatively long period (Fountoulakis et al., 2007; Burgi, 2010; Henjum et al., 2010). No different from iodine deficiency, excess iodine is also risk to health, such as lead thyroiditis, hyperthyroidism, hypothyroidism, goiter (Henjum et al., 2010) and the various impacts with various manifestations, such as increased pulse rate, weight loss, excessive sweating and tremor.

Several studies have found, the case of excess iodine in endemic areas, such as Alsayed et al., (2008) found 54.8% of women in Egypt, suffered excess iodine and correlated with subclinical hypothyroid condition. Mutalazimah and Asyanti (2010), urinary iodine measurement of primary school students, in Cangkringan, Sleman, showed iodine excess of 10%. Henjum et al., (2010) showed a very extreme, ie, finding 84% of school children in endemic areas Saharawi experiencing excess iodine. Mutalazimah (2013) found cases of subclinical hyperthyroidism, in women of reproductive age in endemic areas of iodine deficiency by 26%. This study supported by Hermann et al., (2004) and Lamfon (2008) about the existence of subclinical hyperthyroidism, which is marked by the tendency of decrease in serum thyroid stimulating hormone (TSH), on the subject in endemic areas of iodine deficiency.

Various problems related to iodine and thyroid in adult groups, occur 4-10 times more often in women than men, especially during the reproductive age (Strieder et al., 2003; Gonen et al., 2004; Fountoulakis et al., 2007; Lamfon, 2008; Watt, 2009). Based on the data that women are more susceptible to disruption of thyroid function, so it is recommended to perform screening in women on a regular basis, especially those aged over 35 years, even the

younger the better to prepare for pregnancy (Glinioer, 2008; Stockigt, 2010).

In Indonesia, screening measurement using of urinary iodine, TSH and FT4, felt very expensive. There is a shortage of screening methods thyroid dysfunction by measurement of SE, led to the discovery of a case to be less accurate, since SE cannot distinguish between hypothyroidism and hyperthyroidism. Thus are blurring the intervention measures prevention of iodine deficiency as a cause of hypothyroidism and hyperthyroidism. Comprehensive the instruments screening reveals more detail and specific the symptom with thyroid disorder. The instruments are developed through elaboration of other symptoms in addition to SE.

Several studies on the association of thyroid disorders and symptoms such biopsychosocial, strengthen the basis for researchers to develop a questionnaire called the TDQ, aims to be an alternative measurement tool for screening for thyroid disorders including hypothyroidism in women of child bearing age. TDQ developed through a series of instrument construction process, from the identification of items, expert justification, content validity testing, to test the validity and reliability. As a screening instrument, TDQ must qualify, not only more comprehensive and proven reliability, but also must meet several criteria for diagnostic tests, ie the value of the diagnostic is not much different from diagnostic testing standards, provide more convenience for the patient, easier and simpler (user friendly), cheaper, and can diagnose in the early phase (Sastroasmoro and Ishmael, 2011; Knottnerus, 2002; Dopson and Fitzgerald, 2006; Mc.Dowell, 2006; Mayer, 2010).

In line with this, Mahfoud et al., (2011) reported the results of his research, that the development and validation of a question-

naire for the screening, is the first step in an effort to further diagnosis. Thus, this study aims to perform diagnostic tests TDQ, which includes the values of precision and accuracy through analysis of percent agreement (PA), the coefficient of Kappa, Se, Sp, LR (+), LR (-), the index Youden, AUC on the curve ROC and DOR.

### SUBJECTS AND METHOD

This was a diagnostic study with cross sectional design. Population were all women aged 18-45 years in endemic areas of iodine deficiency, while the source population is women aged 18-45 years living in Gayamharjo, Wukirharjo and Sumberharjo, Prambanan, at 2,760 Childbearing age women.

Application of sample size calculation method, had the formula for the case of the population, and obtained 112 WUS subject, taken at random by simple random sampling technique. Scores obtained using TDQ hyperthyroidism through interviews and examination of signs and symptoms of the

subject, with the range of scores ranging from 0 - 158.

As the gold standard, measurement of TSH and FT4 by trained analysts biochemistry and analyzed in the laboratory department of clinical pathology Dr. Sardjito. Hyperthyroidism interpreted if TSH <0.4 µU/ l, or FT4 levels > 2.1 ng / dl.

Analysis of diagnostic tests was using analytical precision with percent agreement (PA) and the Kappa coefficient, and analysis accuracy with Se, Sp, LR (+), LR (-), Youden index, the AUC ROC curve and BANG.

### RESULTS

Measurement of TSH and FT4 showed that subjects with hyperthyroidism by 31 (27.7%) and normotiroid by 81 (72.3%). TDQ score for hyperthyroidism, are in the range 8-113, to interpret the threshold scores are used determine the indication subject suffering from hyperthyroidism, then do exploration on several scores of hyperthyroidism, using a threshold score of 20, 30, 40, 50, 60 and 70.

**Table 1. Correlation test TDS-FT4 and TSH on the subject of hyperthyroidism**

Threshold	TDQ	TSH-FT4		PA	Kappa	P
		Hipertiroid n (%)	Normal n (%)			
20	Hipertiroid	29 (54.7)	24 (45.3)	58.8	0.43	< 0.001
	Normal	26 (31.3)	30 (93.8)			
30	Hipertiroid	28 (59.6)	19 (40.4)	74.1	0.49	< 0.001
	Normal	3 (7.9)	35 (92.1)			
40	Hipertiroid	28 (68.3)	13 (31.7)	81.2	0.62	< 0.001
	Normal	3 (6.8)	41 (93.2)			
50	Hipertiroid	26 (66.7)	13 (33.3)	78.8	0.57	< 0.001
	Normal	5 (10.9)	41 (89.1)			
60	Hipertiroid	21 (70.0)	9 (30.0)	77.6	0.51	< 0.001
	Normal	10 (18.2)	45 (81.8)			
70	Hipertiroid	11 (68.7)	5 (31.3)	70.6	0.29	0.005
	Normal	20 (29.0)	49 (71.0)			

Furthermore, category thyroid status based on scores TDQ and categories of thyroid status by TSH-FT4 at each threshold

scores, presented in contingency tables 2x2 and analyzed values of precision diagnostics, the agreements diagnosis of hyperthy-

roidism between TDQ and TSH-FT4 through value PA and the Kappa coefficient, and correlation analysis using chi square (Table 1). In addition to the values of precision, table 2x2 is also used as the basis for calculating the values of diagnostic accuracy that includes Se, Sp, LR (+), LR (-), the index Youden, AUC in the ROC curve and BANG, the summary results of the analysis can be seen in Table 2.

Table 1 seen agreement between TDQ and TSH-FT4 in determining thyroid status of the subject, which measured by the value

of pa, varied range between 58.8 to 81.2%; while the Kappa coefficients ranged from 0.29 to 0.62. p value of the chi square test showed that all threshold score correlated between TDQ-FT4 and TSH (<0.05).

Table 1 also shows the comparison of the values of precision, the best value is on the threshold score TDQ 40, namely with PA 81.2% and Kappa coefficient of 0.62.

Summary results of the analysis of precision and accuracy of a diagnostic test for hyperthyroidism TDQ at various thresholds can be seen in Table 2.

**Table 2. Summary of the results of a diagnostic test for hyperthyroidism TDQ**

Threshold	PA	Kappa	Se (%)	Sp (%)	LR +	LR -	Youden Index	AUC	DOR
20	58.8	0.43	94	56	2.14	0.10	0.50	0.746	21.4
30	74.1	0.49	90	65	2.57	0.15	0.55	0.776	17.1
<b>40*</b>	<b>81.2</b>	<b>0.62</b>	<b>90</b>	<b>76</b>	<b>3.75</b>	<b>0.13</b>	<b>0.66</b>	<b>0.831</b>	<b>28.8</b>
50	78.8	0.57	84	76	3.50	0.21	0.60	0.799	16.7
60	77.6	0.51	68	84	4.25	0.38	0.52	0.755	11.2
70	70.6	0.29	36	91	4.00	0.70	0.27	0.631	5.7

Table 2 various indicators of precision and accuracy score of hyperthyroidism, which varies. There are quite accurate, there is also inaccurate. The use of various indicators in this study, is intended to get the value of the threshold score TDQ for hyperthyroidism, the most optimal namely score of 40. In addition to having Kappa coefficient value PA and the highest score of 40 also produces value Se, Sp, LR (+), LR (-), Youden index, ROC curves and the AUC in the most optimal BANG ie 90% respectively; 76%; 3.75; 0.13; 0.66; 0.831 and 28.8.

## DISCUSSION

### A. Value PA and Kappa coefficient

Percent agreement also commonly referred to as an overall percent agreement. It obtained by dividing the number of frequen-

cies of the pair observation cell on the first test and the second test. The cell true positive and negative with the total number of observations or by formula percent agreement=  $(a+d) / (a+b+c+d) \times 100\%$  (Biswas, 2006; Bruno et al., 2010). Kappa coefficients for dichotomous data is calculated using the formula;  $\kappa = (po-pe) / (1.0-pe)$ , which is  $po = (a + d) / (a + b + c + d)$  and  $pe = [ \{(a + b) / n\} \times \{(a + c) / n\} + \{(c + d) / n\} \times \{(b + d) / n\} ]$ . Interpretation Kappa coefficient of agreement >0.75= Very Good; 0.40-0.75= Good; <0.40= Weak (Murti, 1996; Szklo and Nieto, 20017). The higher the p and the Kappa coefficient, it is dealing TDQ and TSH-FT4, in diagnosing hyperthyroidism. Table 2 showed that pa is varied, with the highest value (81.2%) on the threshold score of 40, and the threshold scores

>40, the value becomes lower. Most threshold score TDQ, showed Kappa coefficients were classified as good and not found a very good category. Interpretation Kappa coefficient on the diagnostic test of hyperthyroidism is included in both categories with the highest value reached 0.62 on a threshold score of 40.

### **B. Sensitivity, specificity and Youden index**

Sensitivity is the ability of measuring instrument to recognize a sore subject. The sensitivity and specificity of an indicator of the intensity a positive and negative test when applied to the subjects, both of which have unknown status or not (Davidson, 2002). According to the table 2x2, the formula calculate the accuracy of diagnostic test; sensitivity=  $a/(a+c)$  and specificity=  $d/(b+d)$ . Sensitivity and specificity can also be correlated, of course, a negative correlation with the results, because if the increased sensitivity, the specificity will decrease, and vice versa (Verhagen et al., 2008).

Sensitivity indicates the proportion of subjects with positives results, both on TDQ-FT4 and TSH measurements. Table 2., show the sensitivity of the diagnostic test of hyperthyroidism varies from 36-94%, increase were based on a threshold score decreased. The specificity is the ability of a diagnostic test to determine that the subject does not hurt. That is, the specificity is the proportion of subjects with a negative result, both TDQ-FT4 and TSH measurement.

Interval specificity in diagnostic tests for hyperthyroidism TDQ this, ranging from 56-91%, which increases with the increase in the threshold score. The highest sensitivity value of 94 was obtained at a threshold score of 20. When combined with specificity, the sensitivity values are optimal with the specificity, obtained in the threshold score of 40. Youden index has a minimum

and maximum value from -1 to 1. A value of 1 represents the optimum value for an algorithm (Bohning et al., 2008). Thus, the Youden index, with the highest (0.66) obtained at the threshold score of 40. These results confirm that three indicators, the threshold, score of 40 selected optimal.

### **C. LR (+), LR (-) and DOR**

LR calculation using the following formula, LR (+) = sensitivity / (1-specificity), LR (-) = (1-sensitivity)/ specificity (Davidson, 2002, Indra et al., 2004). LR shows that pre-test and posttest change probability, the interpretation as follows (Indra et al., 2004; Elavunkal and Sinert , 2009) LR (+) > 10 or LR (-) < 0.1 produces changes very large (excellent); LR (+) between 5-10 and LR (-) between 0.1-0.2 produce big changes (very good); LR (+) between 2-5 and LR (-) between 0.5 to 0.2 generate moderate changes (fair), whereas LR (+) between 1-2 and LR (-) between 0.5-1 produce change small (useless).

Value LR (+) and LR (-) on all threshold score TDQ for hyperthyroid, showed mixed results from a small change, until major changes to the pre-test to post-test probability. Tests on the LR even this value, producing the best choice there is on the threshold score TDQ 40. Although LR (+) is not the highest, and LR (-) not the lowest, but the combination of LR (+) is quite large (3.75) and LR (-) small (0.13), the most optimal compared to a threshold score of others. This indicates that TDQ helpful enough to change the pre-test probability, so TDQ can be useful for screening for thyroid dysfunction, especially hyperthyroidism. Similarly, the value of DOR, the TDQ testing for hyperthyroidism, shows all valued threshold score value > 1, with a highest score of 28.8 was also obtained on the threshold score of 40, meaning that the value of the DOR, TDQ performance as a

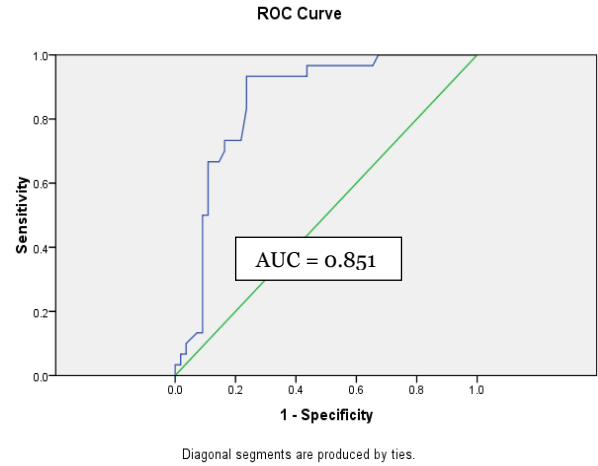
function of screening hyperthyroidism, quite good.

**D. AUC and ROC curves**

The area under the ROC curve, or commonly referred to as area under the curve (AUC), indicating the size of the overall performance of a diagnostic test. The bigger ROC triangle, optimize combination of sensitivity and specificity (Jones and Athanasiou, 2005; Akobeng, 2007). ROC curve analysis is also a method used to evaluate the logistic regression model. This analysis calculated the strength of the predictive value of the model to distinguish between positive and negative cases. It is calculated by AUC wide. As the AUC wide c-statistic or concordance index, a value that varies from 0.5 meaning no discriminatory power, up to 1.0, which means having the perfect discriminatory power (Cook, 2008).

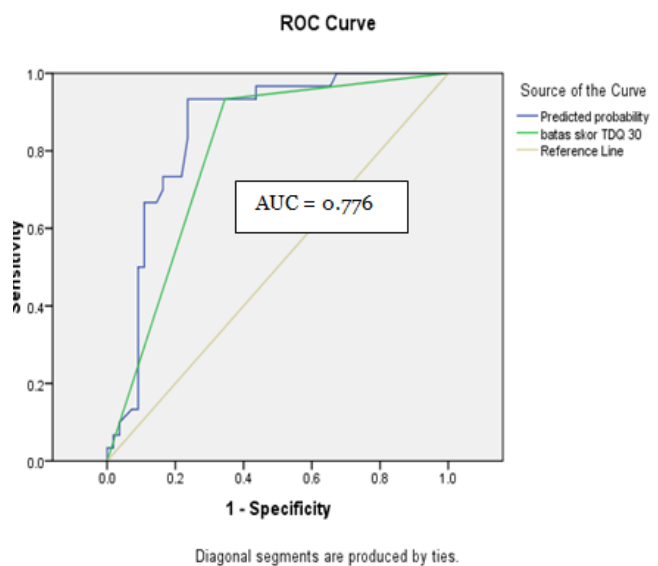
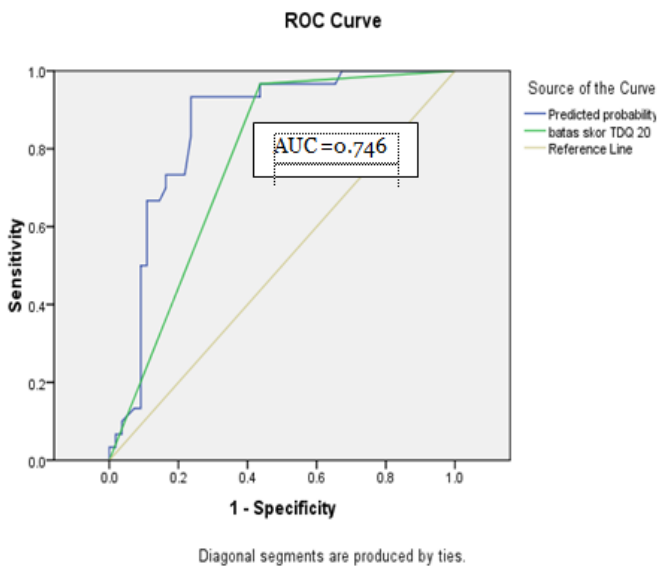
The resulting comprehensive AUC of the ROC curve, the accuracy test for hyperthyroidism TDQ at various threshold score TDQ this, ranging from 0.631 to 0.831 ROC (Picture 2). Comparative curves (Picture 1),

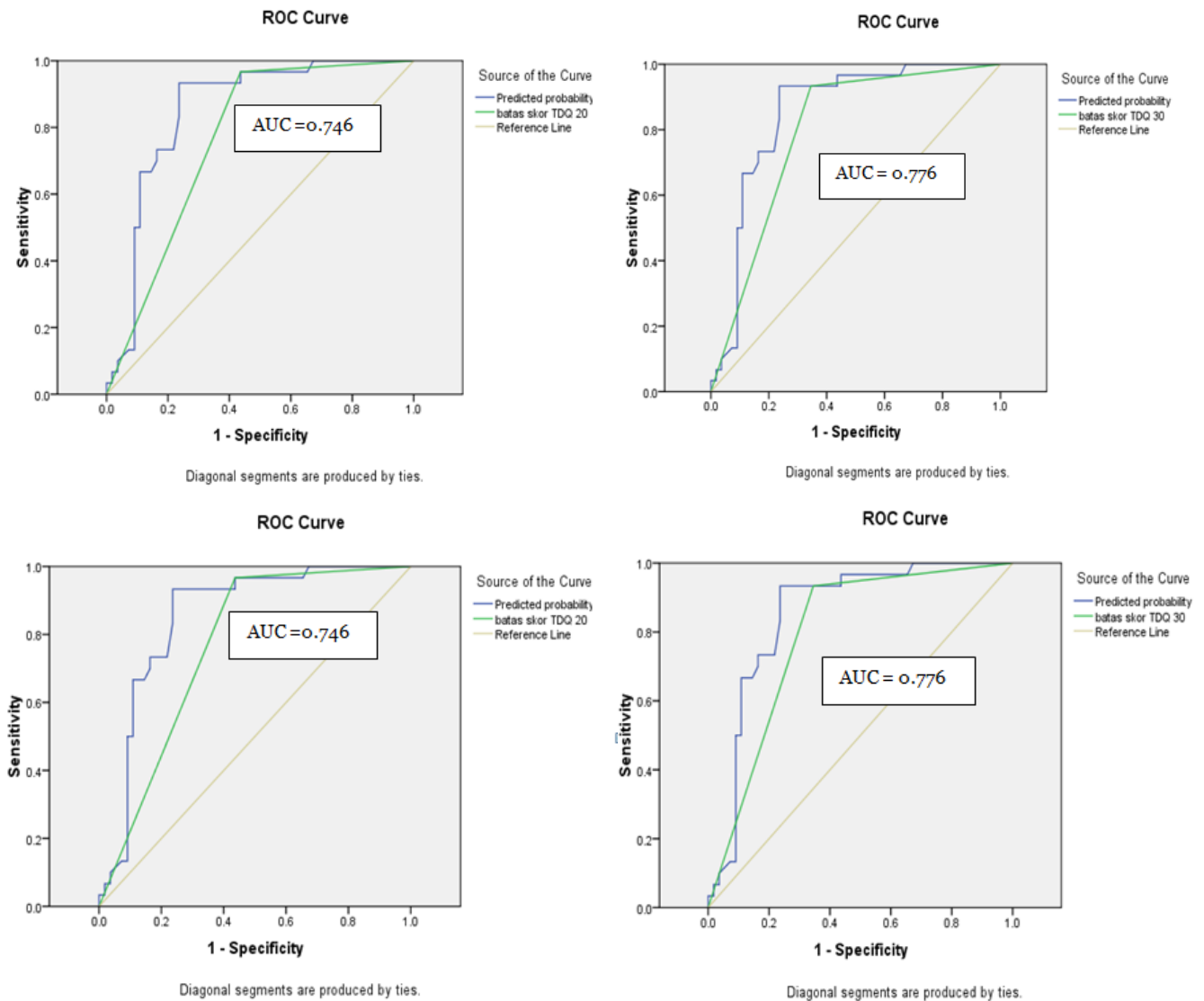
set up under the assumption prediction score TDQ for hyperthyroid against thyroid status, using logistic regression test basis (prediction probability).



**Picture 1. ROC curve hyperthyroid score TDQ as predicted probability**

Picture 1 shows that the vast reaches 0.851 and the AUC will become a standard benchmark, which will be used to compare the AUC on a wide variety of scores TDQ threshold for hyperthyroidism (Picture 2).





**Picture 2. ROC curves at various threshold score TDQ for hyperthyroidism**

Based on the images of ROC curves at various threshold score TDQ for hyperthyroidism (Picture 2), each comprehensive look AUC, can add justification to determine the basis of the interpretation of the election threshold score, earning the most accurate diagnostic test. The AUC vast increase of the threshold score of 20, 30 and wide reaching the highest (0.831) was obtained from the threshold score of 40 and decreased again at a score of 50, 60 and 70. Size  $AUC > 0.8$ , generally indicates that the test is accurate, and more close to the curve at the top left corner, which is the point (0, 1) the more

accurate. The larger AUC makes more accurate diagnostic test (Jones and Athanasiou, 2005; Chaudron et al., 2010). However, for screening purposes, the value of higher sensitivity is preferred, although the AUC have the same size.

Interpretation threshold score of hyperthyroidism, such as the indicators, the *p*value Kappa coefficient, Se, Sp, LR +LR-, Youden index and DOR. The value of the optimum accuracy and the best obtained from the threshold score of 40 and was adequate as a threshold determination of the diagnosis of hyperthyroidism score

TDQ. The vast AUC on the threshold score of 40 is the highest, but it also evaluates Youden index, Kappa coefficient and LR (+) and LR (-), which is enough to show the accuracy. For institution involved to make the results of this study into policy input program updating data related to iodine deficiency and thyroid disorders through routine screening and sustainable.

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