Administered Activity and Fluids Intake as Predictors of Shorter Isolation Time for Low Risk Papillary Thyroid Cancer Patients Undergoing Radioactive Iodine Therapy

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Abstract ***Objectives:*** Patients upon admission in the isolation ward to be treated with radioactive iodine for thyroid cancer post ablation are instructed to drink plenty of water in order to shorten the length of stay at the hospital and to be discharged in a timely manner. ***Methods:*** Logistic regression (LR) was used to analyze the multivariable data and to propose a logistic regression model (LRM) that can predict the probability of the patient to be isolated for shorter time taking into account the administered activity in [MBq] and the total volume in [ml] of fluids consumed during his stay. ***Results:*** The proposed logistic regression model is: Log (odds) = -3.9931 + 0.0007*(fluids intake in [ml]) + .0011*(administered activity in [MBq]). This model has an area under the ROC curve of 0.70 and false positive rate of 0.34 or (specificity= .66) and true positive rate or (sensitivity) of 0.68. The model may help organizing the ward assignment and allows better planed radiation protection aspects of the procedure. ***Conclusions:*** The presented method can be used to analyze variables related to a binary outcome like short or long isolation time and also to predict the probability of the outcome before the start of the procedure once we know the administered activity and the amount of fluids that the patients will consume during his or her stay in the ward.

Keywords Papillary thyroid cancer, Radioactive Iodine treatment, Isolation time, Logistic regression model

1. Introduction

For thyroid cancer patients undergoing radioactive iodine therapy (RIT) the release from hospital confinement is possible when the radiation dose levels emitted from the patient are below national regulatory permissible levels or the remaining radioactive iodine in their bodies are below a certain regulatory defined amount, in the kingdom of Saudi Arabia it is 1100 MBq. Upon admission to the ward the patients are given the instructions to drink plenty of water and fluids, also to void their urinary bladder frequently in order to reduce their hospitalization time and reduce internal radiation exposure to other body organs such as the bladder and the bone marrow. It is known that radioactive iodine (RI) is eliminated from the body mainly through the urine.

It has been hypothesized that renal deficiency may lead to slower iodine-131 excretion rate from the patients leading to longer isolation time in the ward [1].

Renal dysfunction has been associated with larger serum creatinine values. Also serum creatinine has been used in the calculation of the estimated glomerular filtration rate (eGFR), therefore examination of the relationship between the patient serum creatinine level and shorter isolation time (IT) is kind of rational path to explore.

In a recent study, it has been shown that patient using high fluid intake, more than 60 ml/hr, alone would not effectively reduce the patient's radiation dose rate at least not more than a well-hydrated state [2]. This observation suggest that there are other factors contributing to faster biological iodine release from the patients bodies and therefore a shorter IT.

Another study demonstrated that patients in a hypothyroid phase of more than four weeks may have a decreased GFR and they could probably have a longer whole body effective half-life than others [3].

We are interested to find out if drinking plenty of fluids is correlated with shorter IT or there might be other factors also contributing to shorten the IT. This study included a total of 218 patients, 165 females and 53 males low risk thyroid cancer patients all diagnosed with papillary thyroid carcinoma (PTC). All these patients had no distant metastases prior of being admitted to RIT.

Binary logistic regression analysis method was used to analyze a number of variables that were available to us for this study namely: serum creatinine, urea, administered activity and the amount of fluids consumed during their stay

in the isolation room in the ward. The results of this work have several potential implications regarding radiation protection planning and management of papillary thyroid cancer (PTC) patients treated with radioactive iodine in hospitals.

For example; patients with higher probability for a long isolation time (IT) can be admitted to the ward over the weekend and the others during the week days. This will allow radiation protection staff not to be present in the hospital over the weekend to release the patients with potential longer IT period.

After searching the literature and to the best of our knowledge there were a very limited number of studies relating the amount of fluids consumed by the patients and the duration of the IT in the ward for thyroid cancer patients [2,4].

The aim of the study was to find predictors of short IT stay or a logistic regression model to be used to predict the duration of the isolation time, before the start of the RIT and admitting the patient into the ward.

2. Methods

We have logged the total fluids intake for each patient in [ml] and have used this information along with other variables from the patients' files. The variables used in this analysis are: the serum urea in [μmol/L], creatinine in [mmol/L], the administered activity in [MBq] and the length of stay in [hrs].

Binary logistic regression was used to analyze the association between serum urea, creatinine, the administered activity and the amount of fluids intake with the IT. The IT was identified as the dependent variable or the outcome of the study. We had two binary outcomes described as short isolation time less than 31 hours and longer time for more than 31 hours. Table 1 has the patients' data.

Logistic regression modeling

Logistic regression is given by the following relationships

$$\text{Log(odds)} = \text{Log}(p/1-p)$$
$$= B_0 + B_1 x_1 + B_2 x_2 + \ldots\ldots + B_n x_n \quad (1)$$
$$P = \text{Exp}(B_0 + B_1 x_1 + B_2 x_2 + \ldots\ldots + B_n x_n)/1$$
$$+ \text{Exp}(a_0 + B_1 x_1 + B_2 x_2 + \ldots\ldots + B_n x_n) \quad (2)$$

Where x: are the predicting variables also called independent variables
B: are the model coefficients
B_0: is the intercept
P: is the probability
Odds ratio: = $p/1-p$

Statistical analysis

Figure 1 has a matrix of scatter plots for the main variables used in this work with regards to the IT. We can see from the continuous distribution that we have two groups of patients, the first is a group that has a short IT of less than 31 hours

(n=112) and the second group with IT of more than 31 hours (n=106).

Then the continuous time of stay data were dichotomized into two groups, with a cutoff value of 31 hours separating the two groups short IT for the patients released for hospital confinement in less than 31 hours and a long IT group for those released after more than 31 hours.

Multivariate logistic regression analyses were performed to divulge the variables associated with isolation time of stay in the ward, such time is directly related to the biological elimination of the radioactive iodine from the patients' bodies. Figure 2 has a boxplot representation of the variables used in this research.

All statistical analyses were performed using Matlab R2016b statistics and machine learning toolbox (Natick, MA, United States) software. A p-value of (<0.05) was considered statistically significant.

The research ethics review board (RERB) approved this study. And personal information leading to the identification of the patients' identity has been removed from the main data spread sheet for this research to ensure strict patient confidentiality.

3. Results

We have illustrated a method of analysis popular in both social and medical sciences research aiming at examining the relationship between multiple explanatory or independent variables and a dependent variable binary in nature. Table 2: has the result of the multivariable logistic regression analysis and the model we have found was:

Log (odds) = -3.9931+ 0.0007*(fluids intake in [ml]) + .0011*(administered activity in [MBq]).

Only the administered activity and the fluids intake were found to be significant predictors of the IT.

The model was tested for goodness of fit using a receiver operating characteristic (ROC) curve and by calculating the area under the curve (AUC). Figure 3 has the ROC curve for the obtained model.

To validate the conclusions of this study, more patients' data are required and also studies from different countries and populations.

We have conducted hypothesis testing to see if the data distribution for both the administered activity and the fluids intake for the two groups of IT short (n= 112) and long (n=106) comes from the same distribution.
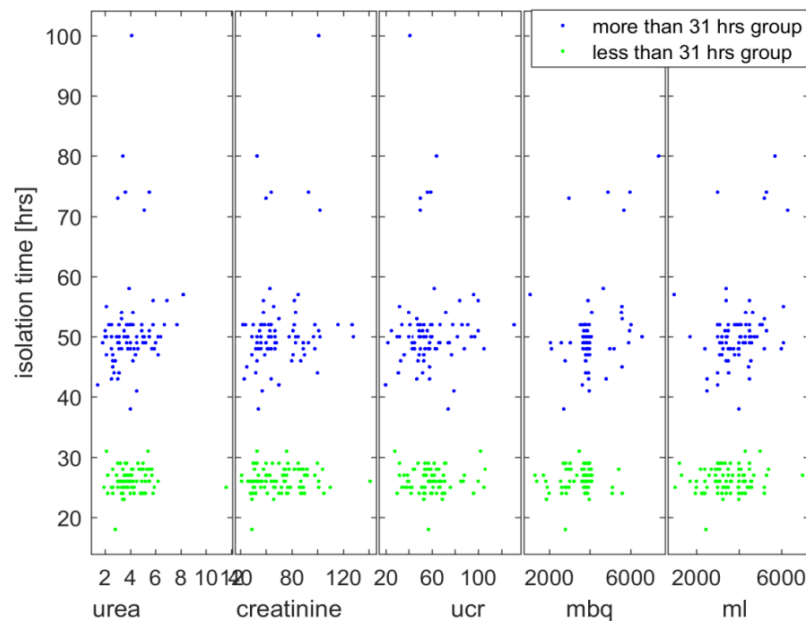
For both groups the administered activity and the fluids intake distributions were skewed (see figures 2a, 2b), and were tested for normality using Jarque-Bera and Lilliefors tests to confirm that the distributions were not following a normal distribution (p value <0.05).

Then the Wilcoxon rank sum test was used to verify the hypothesis that the median value of the administered activity in the short IT group is different from the long IT group and the amount of fluids intake for the short group is different
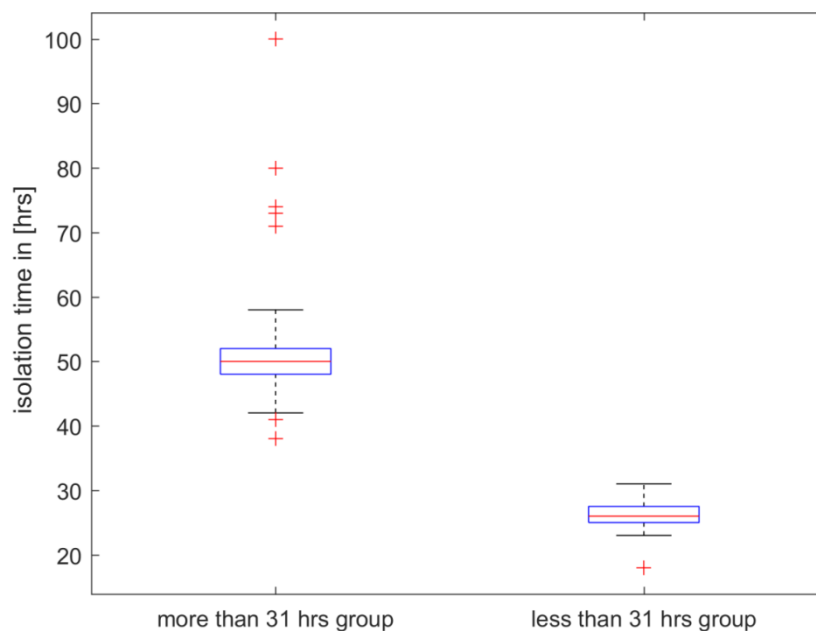
from the long group (p value < 0.05). The test results confirmed that there was a statistically significant difference among the two groups for the administered activity (p<0.01) and for the fluids intake (p=0.04).

Table 1. Patient data summary: The table includes the data of the variables analyzed in this work and it refers to 218 patients 165 females and 53 males
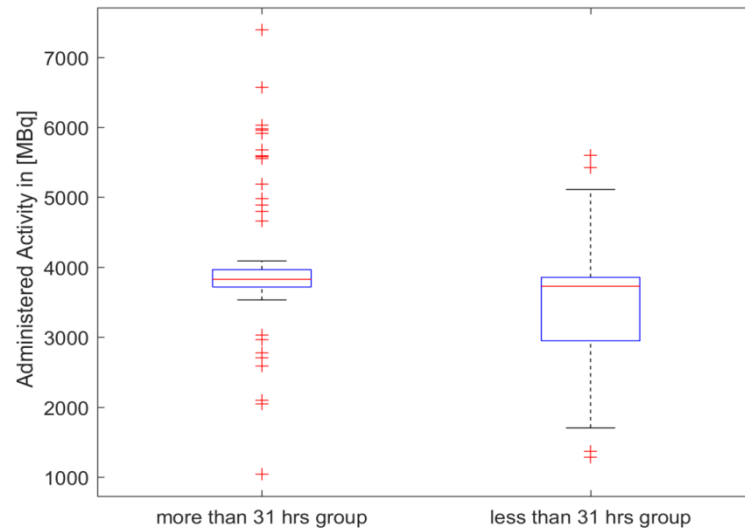
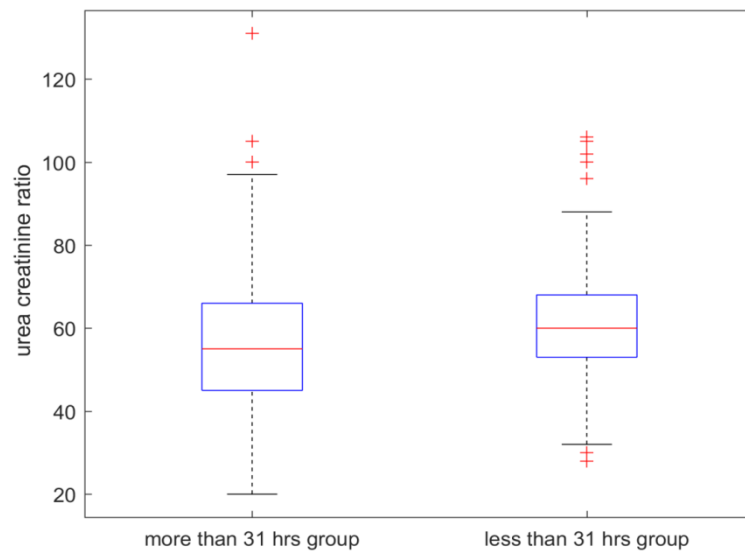| Variables	median	maximum	minimum	Standard deviation
Administered activity [MBq]	3799	7390	1046	896
Fluids intake [ml]	3850	7000	950	1074
Serum urea [μmol/L]	3.8	11.6	1.4	1.4
Serum creatinine [mmol/L]	64	141	41	19
Urea/creatinine ratio	58	130	20	18
Isolation time [hrs]	29	100	18	14

Figure 1. Group scatter matrix showing the 218 patients data distribution for 5 variables used in the analysis. In the figure above the abbreviations used are as follows: Urea: Serum urea in [mmol/L], creatinine: serum creatinine in [μmol/L], mbq: is the administered activity in [MBq], ml: fluids intake in [ml]

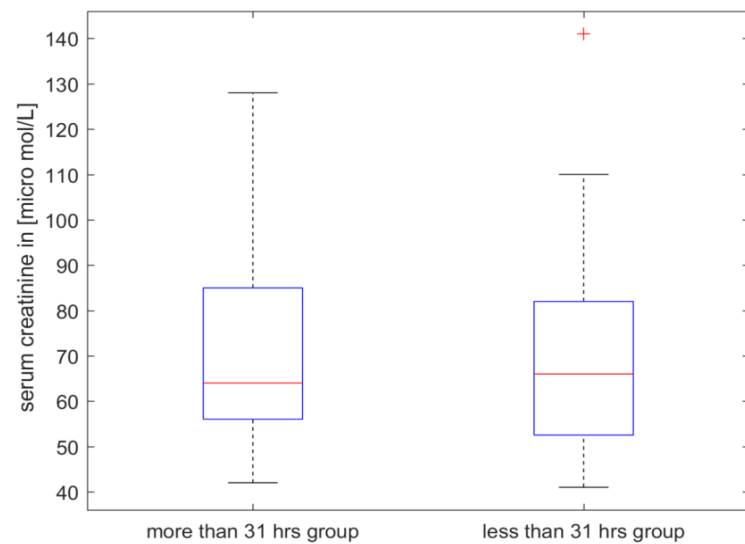
Figure 2(a). Boxplot showing the isolation time in [hrs] for the 2 groups of isolation time in this study (n=218) patients

Figure 2(b). Boxplot showing the administered activity in [MBq] distribution for the 2 groups of isolation time in this study (n=218) patients

Figure 2(c). Boxplot showing the urea/creatinine ratio distribution for the 2 groups of isolation time in this study (n=218) patients
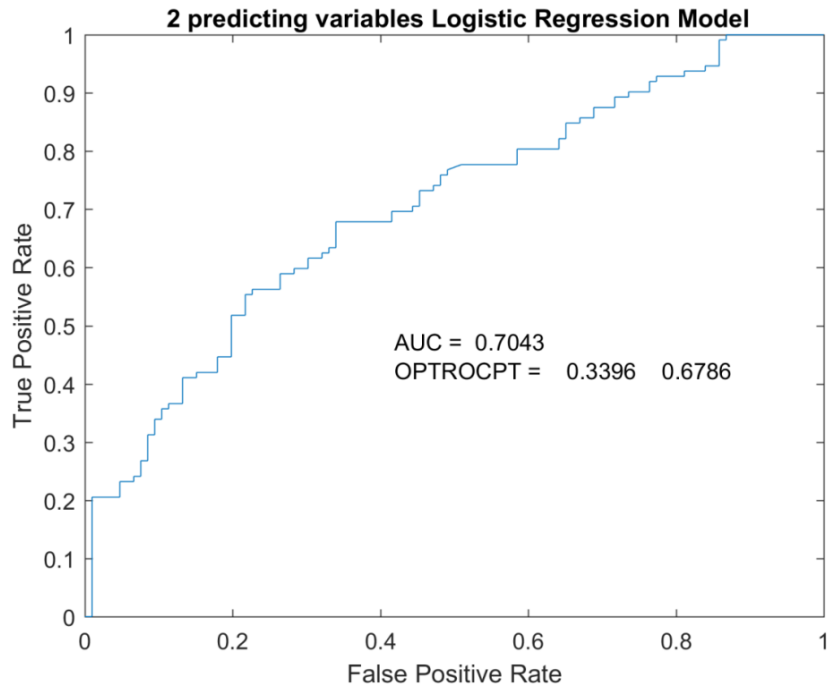

Figure 2(d). Boxplot showing the creatinine distribution for the 2 groups of isolation time in this study (n=218) patients

Table 2. This table summarizes the different models obtained in this analysis and the selection of the last one in the table having two predicting variables only

*	B	UL	LL	P VALUE	SE	Odds	AUC ROC	FPR	TPR
INTERCEPT	**-6.1433**	-1.6582	-10.63	0.0073	2.2883	0.0021	0.6987	0.2804	0.6036
UCR	0.0280	0.0877	-0.032	0.3580	0.0304	1.0284			
CRE	0.0334	0.0833	-0.017	**0.1904**	0.0255	1.0340			
UR	-0.4226	0.414	-1.259	0.3221	0.4268	0.6553			
ML	0.0003	0.0006	0.0000	**0.0317**	0.0002	1.0003			
MBq	0.0007	0.0011	0.0003	**0.0011**	0.0002	1.0007			
GEND	-0.3514	0.4934	-1.196	0.4149	0.431	0.7037			
INTERCEPT	-3.9217	-1.3602	-6.4832	0.0027	1.3069	0.0198	0.6907	0.2710	0.5946
UCR	-0.0023	0.0147	-0.0192	0.7937	0.0087	0.9977			
CRE	0.0040	0.0199	-0.0119	0.6224	0.0081	1.0040			
ML	0.0003	0.0006	0.0000	**0.0260**	0.0002	1.0003			
MBQ	0.0007	0.0011	0.0002	**0.0019**	0.0002	1.0007			
INTERCEPT	-4.1340	-2.1206	-6.1474	0.0001	1.0272	0.0160	0.6905	0.2897	0.6036
CRE	0.0047	0.0197	-0.0103	0.5376	0.0077	1.0047			
ML	0.0003	0.0007	0.0000	**0.0251**	0.0002	1.0003			
MBQ	0.0007	0.0011	0.0003	**0.0016**	0.0002	1.0007			
INTERCEPT	-3.9931	-2.2766	-5.7096	0.0000	0.8758	0.0184	**0.7043**	**0.3396**	**0.6786**
MBq	0.0011	0.0011	0.0003	0.0011	0.0002	1.0011			
ML	0.0007	0.0007	0.0001	0.0222	0.0002	1.0007			

[*]UCR: urea/creatinine ratio, CRE: serum creatinine in [μmol/L], UR: serum urea in [mmol/L],ML: fluids intake in[ml], MBq: administered activity in [MBq], GEND: gender [Male/Female].

The proposed logistic regression model for the probability of having a patient in isolation for less than 31 hours is given by:

Log (odds) = -3.9931+ 0.0007*(fluids intake in [ml]) + .0011*(administered activity in [MBq]).

Figure 3. The ROC curve for the proposed logistic regression model: The area under the ROC curve was estimated as 0.7043 with optimum ROC point of (false positive rate = 0.3396 and true positive rate = 0.6786)

4. Discussion

Logistic regression analysis found no significant correlation among urea, creatinine and urea creatinine ratio (see Table 2) and shorter isolation time in the ward or faster clearance of Iodine. This observation is in agreement with other two studies in which the authors recommend the conduct of further studies to elucidate the effect of renal insufficiency on the radioactive iodine clearance during RIT [1,5]. These studies aimed at finding a mathematical model suggesting reducing the administered activity of the radioiodine in patients with renal insufficiency.

Study and review of factors influencing the thyroid cancer patients LOS during RAT has many advantages among the potential advantages, cost savings, hospital staff radiation protection, comfort of the patient and his family and better bed utilization in busy healthcare facilities.

There are a number of factors affecting the biological half-live of radioiodine in papillary thyroid cancer (PTC) patient undergoing RAIT. The remaining thyroid tissue after thyroidectomy, the patient metabolic activity, the disease extent, the efficiency of the renal system and the liquid intake are among these factors [6].

Metabolism of iodine in thyroid cancer patients and the associated biological elimination from their bodies are directly affecting their isolation time in the ward. Such metabolic activity is subject to many factors and biomarkers. The metabolic activity of radioactive iodine of thyroid cancer patients during RIT vary considerably among patients, the variations include the method of patient preparation before therapy administration [7-10]. Therefore finding a definitive model describing the radioiodine clearance and uptake taking into consideration the wide variability among the individual patients undergoing such therapy is a very complex task and requires further studies.

Among the rare published studies aiming at the effect of fluid intake we can mention the article by (Hoe et al, 2018) They have estimated the minimum amount of fluids needed to reach the release limit in the fastest time possible was about 2103-2148 ml [4]. They also mentioned that 88.2% of their patients can be discharged by 24 hours, and 99.3% by 48 hours of isolation. This study has relatively large number of patients (218) than most of the other studies aiming to study the effective biological half-life [11-13]. The model proposed in this study needs to be tested on a larger number of patients' data for validation.

5. Conclusions

The study helps us managing our patients admitted to the ward for RIT and enhances our radiation safety knowledge related to the local hospital environment.

We have tested the possible correlations of a certain number of variables and the shortness of the length of stay of thyroid papillary thyroid cancer admitted to our medical center for RIT. Proper management of these factors will help improving the wellbeing of the patients and the bed management in the ward and the hospital in general.

In this study we have shown that among the analyzed variables only the administered activity and the amount of fluids consumed during hospitalization may be the best predictors for a shorter time of stay in hospitals for papillary thyroid cancer patients treated for post thyroidectomy remnant ablation radioactive iodine therapy.

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