International Journal of Early Childhood Special Education (INT-JECSE)
DOI: 10.9756/INT-JECSE/V14I2.352 ISSN:1308-5581 Vol 14, Issue 02, 2022

Determining the Association between Serum level of vitamin D and Stage and Grade of Pancreatic Cancer, Ampullary carcinoma and Cholangiocarcinoma

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Abstract

Background: Gastrointestinal (GI) malignancies including pancreatic cancers, periampullary carcinoma and cholangiocarcinoma associated with a high rate of mortality. Finding modifiable risk factors is particularly important to reduce their incidence and associated mortality. Vitamin D and its analogues may play an important role in inhibiting tumor cell proliferation, inducing cell differentiation, or increasing apoptosis. Plasma 25 hydroxy vitamin D biological precursor and active form of vitamin D is the best biomarker for assessing the status of this vitamin in the body. The aim of this study was to evaluate the association between serum level of vitamin D and stage and grade of pancreatic cancer, ampullary carcinoma and cholangiocarcinoma.

Material and methods: All patients with pancreatic cancer, ampullary carcinoma and cholangiocarcinoma referred to Rasul Akram and Firoozgar hospital from March 2019 to December 2020 were enrolled in this study. Demographic data, past medical history, drug history, clinical examination, pathological stage, grade and etc. were extracted from patient's records. Endoscopic ultrasonography (EUS) and fine needle biopsy were done for the cases with suspicious diagnosis of malignancy. The Patients with pancreatic cancer who managed only with chemotherapy, the metastatic cases whose therapy is based on only chemotherapy and the patients died after chemotherapy were excluded from the study. The control group was selected from the patients referred to measuring serum level of vitamin D without a history of pancreatic, ampullary and bile duct diseases, and almost similar in age and sex. Serum level of vitamin D was measured (chemiluminescence immunoassay method) in both case and control group and Vitamin D deficiency was defined as under 30ng/ml in serum. After data collecting statistical analysis was performed using SPSS software Version 23.

Results: Comparing mean serum levels of vitamin D in case and control groups, a significant difference was observed (P-value=<0.001). Moreover 81.8% of patients with lymph node involvement were deficient in vitamin D. Additionally, all patients with grade 3, 90.5% of patients with lymphovascular invasion and 93.3% of patients with perineural invasion were deficient in vitamin D.

Conclusion: Our results showed that there is a significant difference between mean serum levels of vitamin D in case and control groups, as mean serum levels of vitamin D in case group was lower.This study showed that there is a significant association between decreased serum levels of vitamin D and increased risk of pancreatic cancer, ampullary carcinoma and cholangiocarcinoma. Moreover, a significant percentage of patients with perineural invasion, lymph node involvement, and lymphovascular invasion had vitamin D levels less than 30 ng/ml.

Keywords: Serum level of vitamin D, pancreatic cancer, ampullary carcinoma, cholangiocarcinoma.

Introduction

Gastrointestinal cancers including pancreatic cancers, periampullary carcinoma and cholangiocarcinoma are of most diagnosed malignancies in the United States and some of them associated with a high rate of mortality (1, 2). Only less than 5% of patients with GI adenocarcinoma have a five-years survival and most of them expired in six months

after diagnosis. Tumor resection is the only therapeutic choice (3), however more than half of patients do not respond to this treatment at the time of diagnosis, so there is no other effective choice for them (4).
There are different types of pancreatic tumors, but 85-90% of them are pancreatic ductal adenocarcinoma (PDAC), which has a poor prognosis due to inability of diagnose in first stages. Poor prognostic factors include failing to access to the pancreas due to its deep location in the abdominal cavity, delayed clinical manifestations (such as weight loss, epigastric pain, obstructive jaundice) and metastasis detected at the time of diagnosis. Treatment include surgical approach (Whipple procedure), radiotherapy and chemotherapy (5).
In cholangiocarcinoma (CCA) most of patients are not good candidates for resection, considering those with unresectable tumors, prognosis is to bad and they face less than one-year survival (6). Therefore, identifying high-risk individuals for this problem will significantly reduce mortality in this group. There is no screening, molecular test or reliable imaging method for diagnosis of adenocarcinomas in symptomless patients. Due to the need for early detection and diagnosis of malignancy in the prevention or improvement of prognosis, low levels of vitamin D can be considered as a risk factor (7). Vitamin D, a fat-soluble vitamin, correlates with calcium, Phosphate and bone metabolism (8). The best biomarker of Vitamin D status is plasma level of 25-hydroxyvitamin D [25(OH) D], the precursor of Vitamin D and synthesis from sun exposure (9, 10).
There are several studies which demonstrated an inverse correlation between serum Vitamin D level and risk of cancers such as breast (11), colon (12), gastric (13), prostate (14) and others (15). Also, cell cultures and animal studies showed anti tumorigenic effects of Vitamin D (12, 16, 17), and its deficiency caused progression of many types of cancers. Similar studies concluded that vitamin D and its analogues may play an important role in inhibitor of cancer cell proliferation, induce differentiation and promote cell apoptosis in malignancies such as pancreatic, periampullary carcinoma and cholangiocarcinoma (18-23).
So, the aim of this study is to evaluate the correlation between serum level of Vitamin D, staging and grading of ampullary and cholangiocarcinoma of pancreas in patients referred to RasulAkram and Firoozgar hospital, Tehran, Iran.

Materials and Methods

The present study was a prospective cross-sectional study on 88 patients with pancreatic cancers and 88 control group (without history of related diseases, according to self declaratio) with annual measured vitamin D serum level during March 2019 to December 2020 at Rasool Akram Hospital affiliated to Iran University of Medical Sciences. It was designed to evaluate the association between serum level of vitamin D and stage and grade of pancreatic cancers. This study was approved by the Scientific and Ethics Committee of Iran University of Medical Science with reference number of (IR.IUMS.FMD.REC.1399.520).
In this study the principles were considered in all stages. Moreover, researchers have complied with the provisions of the Helsinki and no additional costs have been imposed on patients.
All patients with pancreatic cancers, ampullary and cholangiocarcinoma referred to Rasul Akram and Firoozgar hospital from March 2019 to December 2020 were enrolled in our study. Demographic data, past history, drug history, clinical examination, staging, grading and etc. were extracted from patient's records. Endoscopic ultrasonography (EUS) and fine needle aspiration, was done for the patients with suspicious diagnosis of malignancy. Patients with pancreatic cancer were classified into three groups: resectable, borderline resectable, locally advance.
The first group underwent surgical procedure, the second group underwent surgery after chemotherapy in cases of operable state and the third group only managed with chemotherapy. The third group and also the metastatic cases whose therapy is based on only chemotherapy were excluded from the study. The patients who died after chemotherapy were excluded too. Patients with ampullary carcinoma and cholangiocarcinoma underwent surgical treatment were included in study. The control group was selected from the patients referred to measuring serum level of vitamin D, without a history of chronic diseases, especially pancreatic, ampullary and bile duct diseases in similar age and sex groups. Serum level of vitamin D was measured in both case and control groups. 5 ml venous sample of each patient in both groups was taken and serum level of vitamin D was measured using chemiluminescence immunoassay method. Vitamin D deficiency was defined as serum level of vitamin D under 30ng/ml.

Statistical analysis

The results were expressed as mean and standard deviation (mean ± SD) for quantitative variables and as a percentage for stratified qualitative variables. The t-test was used to compare quantitative variables and the chi-square test was used to compare qualitative variables. We used analysis below of the ROC curve to determine the

cut-off point of the combined index, sensitivity and specificity. Significance level was considered less than 0.05. SPSS software version 23 was used for statistical analysis of data.

Result

A total of 88 patients were enrolled in the study with a mean age of 57.36 (range: 17-76 years). 58 (65.9%) of patients were male and 30(34.1%) were female. There was no significant difference considering age of men and women and the duration of disease among men and women (P-value>0.05). The minimum vitamin D serum level in the study group was 4 ng/ml and the maximum was 55 ng/ml with the average of 15.64 ng/ml. Eighty patients had vitamin D levels below 30 ng/ml. The tumor was adenocarcinoma in 80 patients, including 2 mucinous adenocarcinoma and one signet ring adenocarcinoma, 91.3% of who were deficient in vitamin D serum levels. Seven (87%) out of eight patients with neuroendocrine tumors, were deficient in vitamin D. Also, in 40 patients tumor was located in ampulla of vater, in 37 cases in pancreas and in 37 patients in bile duct, of which 90, 94.6 and 81.8% were deficient in vitamin D, respectively.

A total of 30 patients had perineural invasion, 33 had lymph node involvement, and 21 had lymphovascular invasion. In the study of tumor type, lymph-vascular invasion, lymph node involvement and nerve invasion in each of the tumors of ampulla of vater, pancreas and bile duct, the results were according to Table 1.

Table 1: Frequency of tumor features of patients associated with vitamin D deficiency

		Vitamin D deficiency			
		Yes		No	
		Frequency	Percentage	Frequency	Percentage
Tumor type	Adenocarcinoma	73	91.3%	7	8.8%
	Neuroendocrine tumor	7	87.5%	1	12.5%
Tumor location	Ampulla of vater	36	90.0%	4	10.0%
	Pancreas	35	94.6%	2	5.4%
	Bile duct	9	81.8%	2	18.2%
Neural invasion	No	50	89.3%	6	10.7%
	Yes	28	93.3%	2	6.7%
	Undiagnostic	2	100.0%	0	0.0%
Lymph node involvement	No	51	96.2%	2	3.8%
	Yes	27	81.8%	6	18.2%
	Non-diagnostic	2	100.0%	0	0.0%
Tumor stage	I	1	100.0%	0	0.0%
	II	3	100.0%	0	0.0%
	III	4	66.7%	2	33.3%
	I A	9	100.0%	0	0.0%
	II B	10	100.0%	0	0.0%
	III A	11	78.6%	3	21.4%
	I B	21	95.5%	1	4.5%
	II B	17	94.4%	1	5.6%
	III B	4	80.0%	1	20.0%
Tumor grade	grade1	39	84.8%	7	15.2%
	grade2	33	97.1%	1	2.9%
	grade3	6	100.0%	0	0.0%
	Non-diagnostic	2	100.0%	0	0.0%
Lymph-vascular invasion	No	59	90.8%	6	9.2%
	Yes	19	90.5%	2	9.5%
	Non-diagnostic	2	100.0%	0	0.0%

Two of the patients, who first underwent chemotherapy and then Whipple surgery, had a tumor in the FNA, but after chemotherapy, the Whipple sample was negative in terms of tumor. The tumor size of these two cases was entered from the EUS report. Lymphovascular invasion, perineural invasion, and lymph node involvement were also negative for the tumor, and the stage of the tumor could not be determined.

In the study of the frequency of vitamin D deficiency in patients, the average of vitamin D was 15.64, and considering vitamin D serum level less than 30 ng/ml as deficiency, 90% of patients were deficient in vitamin D.

In univariate study, there was no significant relationship between neither vitamin D deficiency and duration of disease, age, tumor diameter (cm) (using t-test), nor vitamin D deficiency and tumor type, gender, tumor site, perineural/lymphovascular/lymph node involvement, tumor grade and stage (using chi-square test) (P>0.05).

In order to investigate the relationship between the binary response variable of vitamin D deficiency and dependent variables, we used a simple logistic regression model and we calculated unadjusted probability values and confidence intervals and the magnitude of the OR effect or odds ratio (Table 2).

Table 2: Investigate the relationship between the binary response variable of vitamin D deficiency and dependent variables

		B	S.E.	Wald	df	P-value	OR
Step 1[a]	Duration of disease (months)	-0.049	0.097	0.253	1	0.615	0.952
	Tumor type	-1.657	2.019	0.674	1	0.412	0.191
	Tumor location	0.388	0.500	0.602	1	0.438	1.474
	Tumor diameter	0.871	0.482	3.265	1	0.071	2.390
	Lymph-vascular invasion	0.832	1.361	0.373	1	0.541	2.298
	Neural invasion	-1.652	1.440	1.317	1	0.251	0.192
	Lymph node involvement	2.316	1.060	4.771	1	0.029	10.137
	Tumor grade	-2.509	1.263	3.948	1	0.047	0.081
	Tumor stage	-0.231	0.299	0.598	1	0.439	0.793
	Constant	-4.129	2.074	3.963	1	0.047	0.016

a. Variable(s) entered on step 1: Duration of disease (months), Tumor type, Tumor location, Tumor diameter, Lymphovascular invasion, Perineural invasion, Lymph node Involvement, Tumor grade, Tumor stage

Table 2 lists vitamin D deficiency as an independent variable. In this multivariate analysis, there was a significant relationship between lymph node involvement and tumor grade. (P-value<0.05)

The sub-curve area index (AUC) for this model was 0.867, which indicates the high predictive value of the fitted model (Figure 1).

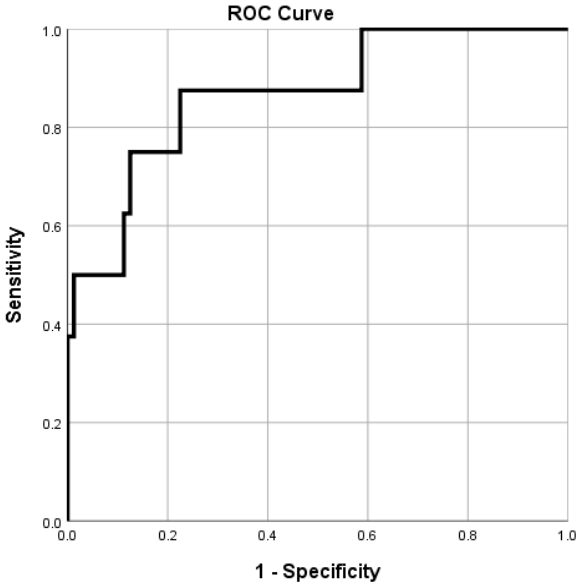

Figure 1: ROC curves for the logistics model

ROC curve was used to determine the best cutting point along with the sensitivity and specificity of vitamin D in predicting the stage of each of pancreatic cancers, ampullary carcinoma and cholangiocarcinoma. In this calculation, point 1 was considered as the best cutting point.
The sub-curve area index (AUC) for this model was 0.667, which indicates the low predictive value of the fitted model (Figure 2)

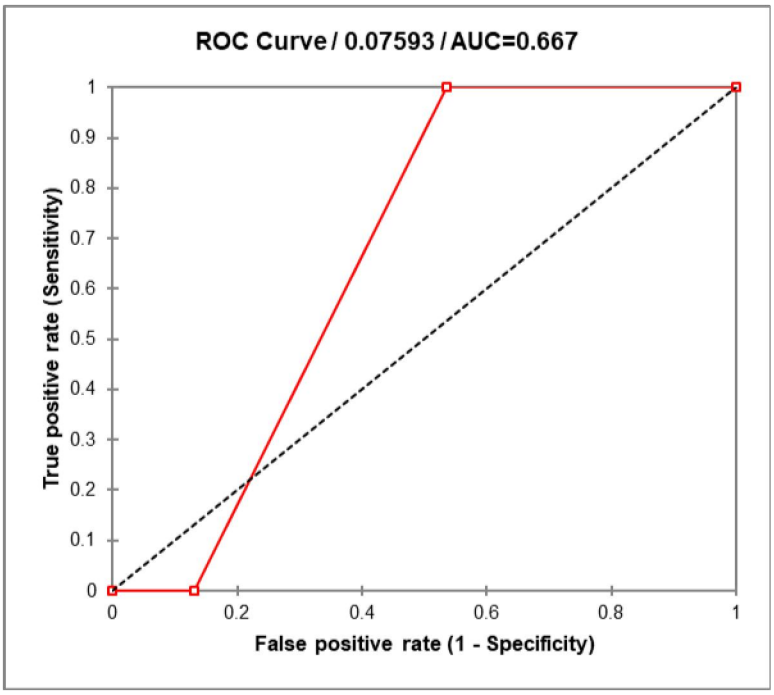

Figure 2. ROC curve to determine the best cutting point along with the sensitivity and specificity of vitamin D in predicting the stage of each of pancreatic cancers, ampullary carcinoma and cholangiocarcinoma

ROC curve was used to determine the best cutting point along with the sensitivity and specificity of vitamin D in predicting the grade of each pancreatic cancer, ampullary carcinoma and cholangiocarcinoma. In this calculation, a point of 0.07 was considered as the best cut-off point. The sub-curve area index (AUC) for this model was 0.543, which indicates the low predictive value of the fitted model (Figure 3).

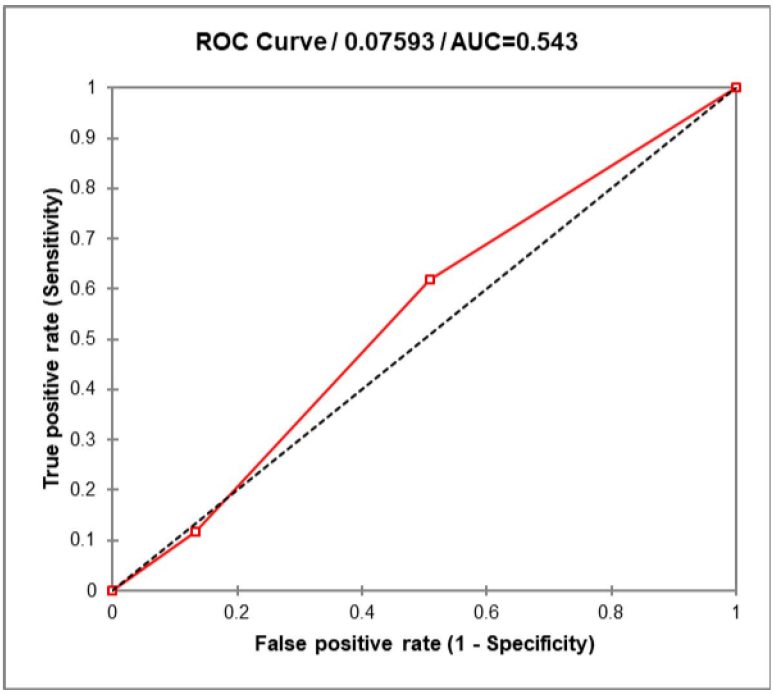

Figure 3. ROC curve to determine the best cutting point along with the sensitivity and specificity of vitamin D in predicting the grade of each pancreatic cancer, ampullary carcinoma and cholangiocarcinoma

Discussion

As a control group, 88 patients without a history of chronic diseases, especially pancreatic, ampullary, and bile duct involvement, with approximately same age and sex as the patient group, whose mean age was 53 (range: 20-77 years) were tested for Blood levels of vitamin D. The frequency of gender of patients was equal to (62.5%) 55 females and (37.5%) 33 males. The minimum vitamin D in the control group was 5.7 and the highest was 63, with an average of 26.6. There was no significant relationship between serum vitamin D levels in men and women. Only 37.5% of controls were deficient in vitamin D.

The tumor was adenocarcinoma in 80 patients, 2 of which were mucinous adenocarcinoma and 1 was Signet ring adenocarcinoma, of whom 91.3% were vitamin D deficient. Of 8 patients with neuroendocrine tumors, 87% were deficient in vitamin D. Tumor was located in 40 patients in ampulla of vater, in 37 cases in pancreas and in 37 patients in bile duct which 90, 94.6 and 81.8% of them were vitamin D deficient respectively.

A total of 30 patients had perineural invasion, 33 had lymph node involvement, and 21 had lymphovascular invasion.

In the study of tumor type, lymphovascular invasion, lymph node involvement and perineural invasion in each of the ampullary, pancreatic and bile duct tumors, the result was that 97.5% of ampullary tumors were adenocarcinoma and 2.5% of them were neuroendocrine type. Only 7% of them had perineural and lymphovascular invasion and 14% had lymph node involvement. Also, 81.1% of tumors located in the pancreas were adenocarcinoma and 18.9% were neuroendocrine; 24.4%, 45.9% and 40.5% of them were associated with lymphovascular, perineural invasion and lymph node involvement, respectively. Also, all tumors located in the bile duct were adenocarcinoma, of which 45.5%, 54.5% and 36.4% were associated with lymphovascular, perineural invasion and lymph node involvement, respectively.

Two patients who first underwent chemotherapy and then Whipple surgery had a tumor in FNA but after chemotherapy, Whipple's sample was negative for the tumor. Tumor size of these two cases was entered from the EUS report. However, because the Whipple sample of these two patients was tumor negative, lymph-vascular invasion, neural invasion, and lymph node involvement, as well as the stage of the tumor, could not be determined. 81.8% of patients with lymph node involvement were deficient in vitamin D.

All patients with grade 3 and 90.5% of patients with lymphovascular invasion and 93.3% of patients with perineural invasion are deficient in vitamin D. In contrast to our study, Cho et al. showed that vitamin D levels could indicate prognosis for patients with advanced pancreatic adenocarcinoma. Vitamin D levels less than 20 ng/ml were poor prognostic factors for stage III and IV patients (24).

There was no significant relationship between vitamin D deficiency and any of other variables. ROC curve was used to determine the best cutting point along with the sensitivity and specificity of serum vitamin D in predicting the stage and grade of each pancreatic cancer, ampullary carcinoma and cholangiocarcinoma. In this calculation, points 1 and 0.07 were considered as the best cutting points, respectively. The sub-curve area index (AUC) was 0.667 and 0.543, respectively, indicating the low predictive value of the fitted model. In this calculation, point 1 was considered as the best cutting point.

The sub-curve area index (AUC) for this model was 0.667, which indicates the low predictive value of the fitted model. There was a significant difference between the mean serum levels of vitamin D in patients and controls. ($P<0.05$)

Comparable to our study, a study by Leon et al found that vitamin K and vitamin D deficiency was common in patients undergoing endoscopic retrograde cholangiopancreatography (25).

In a prospective study by Savio et al., in the gastrointestinal surgery department of Tata Memorial Hospital, patients with periampullary and pancreatic head cancers undergoing therapeutic pancreatoduodenectomy were evaluated for the safety and efficacy of an intramuscular injection of 200,000 international units (5 Mg) cholecalciferol (vitamin D3 Confirmed the safety of muscle vitamin D3 in patients with periampullary and pancreatic cancers (26).

On the other hand, a study by Marina et al. did not support the hypothesis that DBP or serum 25-hydroxyvitamin D has a protective role in pancreatic cancer (25) and in a study by Zhang et al. the results showed that higher levels of vitamin D in patients with pancreatic cancer reduced mortality. However, it had no effect on reducing the incidence of this malignancy (26) Although in vitro experimental study showed the protective effect of vitamin D in pancreatic cancer (29). In another study, 26,916 people were analyzed by Gaks et al.the results showed that people with low plasma 25(OH) D levels had higher cancer deaths, and plasma 25(OH) D levels may affect cancer mortality in a nonlinear relationship (30).

Finally, this study, supported the results of previous studies, showed that there is a significant difference between the mean serum levels of vitamin D between patients and controls. The mean serum level of vitamin D was lower in the group of patients, which could indicate the significant association between decreased serum levels of vitamin D and increased risk of pancreatic cancer, ampullary carcinoma and cholangiocarcinoma. Wolpin et al. conducted a study that evaluated the biochemical prophylaxis of plasma 25 (OH) D levels and showed that higher plasma 25 (OH) D levels were associated with a lower risk of pancreatic cancer (31).

Our study also showed that a significant percentage of patients with neural invasion, lymph node involvement, and lymph-vascular invasion had vitamin D levels less than 30 ng/ml.

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