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The role of BRAF-activated noncoding RNA BANCR in esophageal cancer and its possible use as a molecular marker for prognosis

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BRAF-activated noncoding RNA (BANCR) was found in some studies to act as an oncogene and in others as a tumor suppressor. We aimed to study the role of lncRNA BANCR in esophageal cancer, its expression in cancer tissues, and the plasma of the patients and it's possible to use a non-invasive molecular marker for prognosis and survival. lncRNA BANCR expression was assessed by qRT-PCR in tumor tissues and the plasma of 77 patients with esophageal cancer. lncRNA BANCR was overexpressed in the tumor tissues and the plasma of patients. Its overexpression was significantly linked to adverse clinical and pathological features and short overall survival. In esophageal cancer, lncRNA BANCR was found to act as an oncogene. The expression and specificity of lncRNA BANCR in the plasma of esophageal cancer patients make it a possible prognostic non-invasive molecular marker.

Keywords: esophageal cancer, BANCR, qRT-PCR, tissues, plasma

INTRODUCTION

With little about esophageal cancer (EC) incidence, mortality, and risk factors all over the world. There is a rising frequency of esophageal cancer; worldwide it is the eighth common cancer (Li et al., 2013). In the United States, it is the seventh cause of death among males (Torre el al., 2018). EC is often associated with an adverse 5-year survival ranging from 4% to 40% (Fitzmaurice et al., 2015).

Long noncoding RNA (lncRNA), is a form of non-coding RNA comprising more than 200 nucleotides capable of manipulating gene expression at transcriptional or posttranscriptional stages (Guttman and Rinn, 2012). Studies have shown that lncRNAs engage in a wide spectrum of biological functions, including cell division, apoptosis, differentiation, and progress in the cell cycle (Cheetham et al., 2013; Cheng et al., 2015). Evolving evidence shows that lncRNAs play a significant role in human cancer, which may represent a different but successful approach to dealing with cancer (Gibb et al.,2011). lncRNAs can be used for the detection and prognosis of cancer and can also serve as promising innovative molecular targets for treatment.

BRAF-activated noncoding RNA (BANCR) is located on human chromosome 9, and was first detected in melanoma (Flockhart et al., 2012). Some malignant tumors are abnormally express lncRNA BANCR such as retinoblastoma (Su et al.,, 2015), thyroid carcinoma (Wang et al., 2014),

lung cancer (Jiang et al., 2015), gastric cancer (Zhang et al.,2015), hepatocellular carcinoma (HCC)(Zhou et al., 2015), and, colorectal cancer (CRC) (Shi et al., 2015). The significance of lncRNA BANCR in EC is not completely known.

Therefore, we assessed the clinical significance and role of lncRNA BANCR in 77 patients with EC. We examined its expression levels in the tumor tissues and in the plasma of the patients to assess the possibility of using it as a possible molecular marker. We also examined its relation to prognostic features and survival.

MATERIALS AND METHODS

Seventy-seven patients with EC underwent surgery at the Zagazig University Hospital, Faculty of Medicine, Zagazig University, Egypt and East Jeddah Hospital, Jeddah, SA, and 77 healthy controls, between May 2014 and December 2019 participated in the study. This research was accepted by the ethical boards of the Zagazig University Hospital and East Jeddah Hospital. Informed consent was received from each participant. Clinical staging of all patients was done according to the eighth edition manual of the American Joint Committee of Cancer (AJCC) (Rice et al., 2017).

Blood and Tissue Specimens

Tissue specimens from the EC and their corresponding normal tissues was taken during surgery and stored in liquid nitrogen at -80°C until study time. Five ml of venous blood was collected in ethylene diamine tetraacetic acid (EDTA) containing tubes from all patients before surgery and from the healthy individuals. The collected blood were centrifuged for 5 minutes at 2,000g at 4°C, and then centrifuged again at 12,000 g at 4°C for another 5 minutes to eliminate any cell residue. The supernatant plasma is separated and saved at −80°C until study.

RNA extraction, reverse transcription, and real-time PCR

As shown in company guidelines, we utilized the miRNeasy Mini Kit (Qiagen, Hilden, Germany) to retrieve the total RNA from the tissue samples and the supernatant plasma. A PrimeScript RT Master Mix Kit (TaKaRa, Dalian, China) was employed to synthesize the complementary DNA in a total volume of 50 µL. Quantitative PCR was conducted with SYBR expression assay system (TaKaRa, Dalian, China) using ABI Viia7 (Applied Biosystems, Foster City, CA, USA). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was assigned as the internal control gene since it is relatively stable in the plasma [16]. The sequences of the primes used in this study were: BANCR primers: 5'-ACAGGACTCCATGGCAAACG-3' (forward) and 5'- ATGAAGAAAGCCTGGTGCAGT-3' (reverse), and GAPDH primers: 5'-CGCTCTCTGCTCCTCCTGTTC-3' (forward), 5'–ATCCGTTGACTCCGACCTTCAC-3' (reverse). The PCR reaction was carried out in triplicate and the mean value of the triplicate PCR was used to compute the relative quantity of BANCR according to $2^{-\Delta\Delta Ct}$ model (Schmittgen and Livak , 2008).

Statistical analysis

Statistical analysis was performed with version 16.0 of the SPSS (SPSS Inc., Chicago, IL, USA). Analysis of BANCR expression was carried out by a Student's t-test when comparing two groups and by one-way variance analysis (ANOVA) when comparing more than two groups. The Receiver-Operating Characteristic (ROC) curve was plotted and the area under the ROC curve (AUC) was computed to determine the diagnostic value of BANCR in tissues and plasma. Survival curves are created with the Kaplan-Meier model and correlated with log-rank tests. Variables were regarded as statistically significant when the $P< 0.05$.

RESULTS

lncRNA expression in esophageal cancer tissues and their corresponding normal tissues

In esophageal cancer tissues (ECT), lncRNA was highly expressed relative to their corresponding normal esophageal tissues (NT). It ranged between 11.02 and 24.85 while in NT it ranged between 0.0001 to 5.31. The mean ± SD value of lncRNA expression in ECT was 17.4 ± 3.6 and 1.5 ± 1.02 in NT. This difference in expression was highly significant ($t = 37.07$, $P < 0.0001$).

The receiver operating characteristic (ROC) curve was plotted to evaluate the ability lncRNA BANCR expressions to discriminate between ECT and the corresponding normal tissues, it revealed a high specificity and sensitivity (AUC- = 1.000,95% CI: 1.000 to 1.000, $P < 0.0001$) (Figure 1).

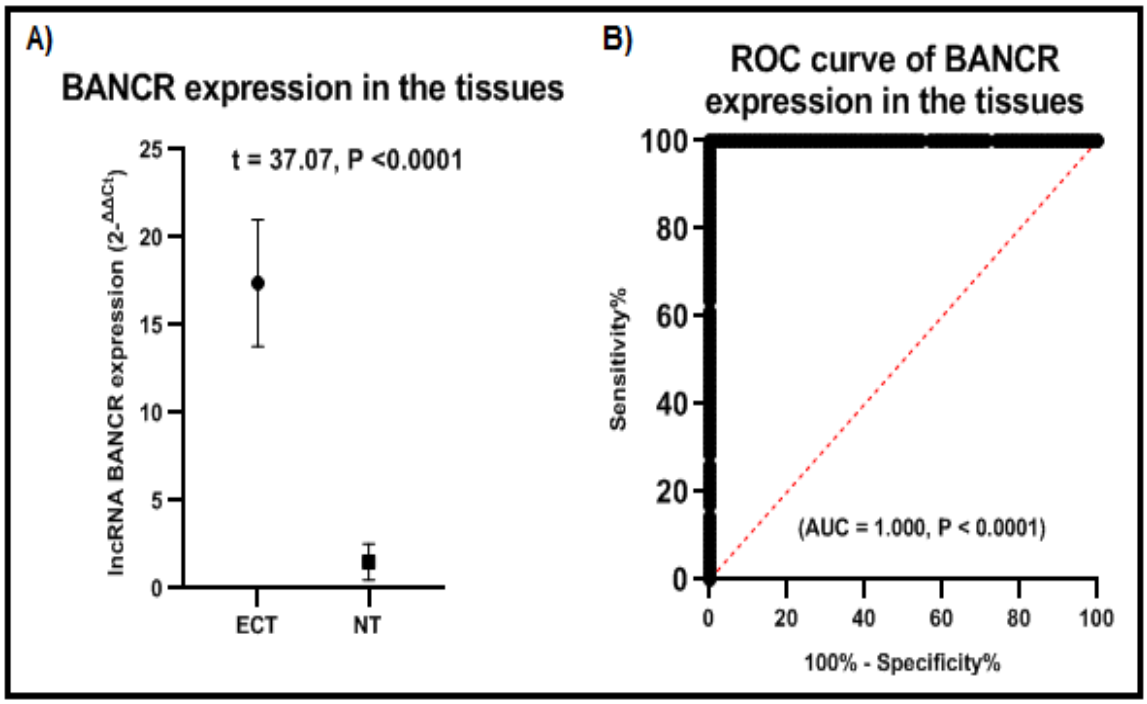

Figure 1: Relative lncRNA BANCR expression levels in the esophageal cancer tissues (ECT) and their diagnostic values

A) lncRNA BANCR expression levels in normal esophageal tissues (NT) and esophageal cancer tissues (ECT) from 77 patients, Student's t test = 37.07, P<0.0001.

B) Receiver operating characteristic curve analysis of lncRNA expression in esophageal cancer tissues for distinguishing it from normal tissues (NT) (AUC = 1.000, 95% CI: 1.000 to 1.000, P<0.0001).

lncRNA expression in the plasma of esophageal cancer patients and the plasma of healthy controls

The lncRNA expression in the plasma was assessed in patients with esophageal cancer and 77 healthy individuals as control. The expression level of lncRNA in the healthy individuals ranged between 0.002 and 4.51 with a mean and SD value of 1.46 ± 0.94, while in the cancer patients, it ranged between 11.12 and 24.84 with a mean ± SD value of 17.34 ± 3.62. This difference in the expression between patients and healthy individuals was highly significant (t = 37.28, P < 0.0001) (Figure 2).

To identify the diagnostic value of the plasma lncRNA BANCR in diagnosis of EC, the ROC curve was carried out between its expression levels in the plasma of patients and its levels in healthy controls, the AUC was 1.000, sensitivity: 100%, specificity: 100%, 95% CI: 1.000 to 1.000, P< 0.0001 (Figure 2).

A-lncRNA BANCR expression levels in the plasma of the healthy controls (HC) and in the plasma of esophageal cancer patients (EC) from 77 patients, Student's t-test = 37.28, P<0.0001.

B-Receiver operating characteristic curve for the specificity of lncRNA expression in the plasma of EC to the HC (AUC = 1.000, 95% CI: 1.000 to 1.000, P<0.0001).

lncRNA expression in the tissues of esophageal cancer and in the plasma

We compared the expression of lncRNA BANCR in both esophageal cancer tissues excised from the patients in their plasma. The mean ± SD value in ECT was 17.4 ± 3.6 in the tissues and 17.34 ± 3.6 in the plasma. The difference in the expression between tissues and plasma was not statistically significant (t = 0.093, P= 0.925) (Figure 3).

We analyzed the relation between lncRNA BANCR expression in the tissues and the plasma by Pearson's correlation revealed a significant correlation between lncRNA BANCR in the plasma of esophageal cancer patients and the tissues of their excised tumors (R2 = 0.992, P< 0.001) (Figure 3).

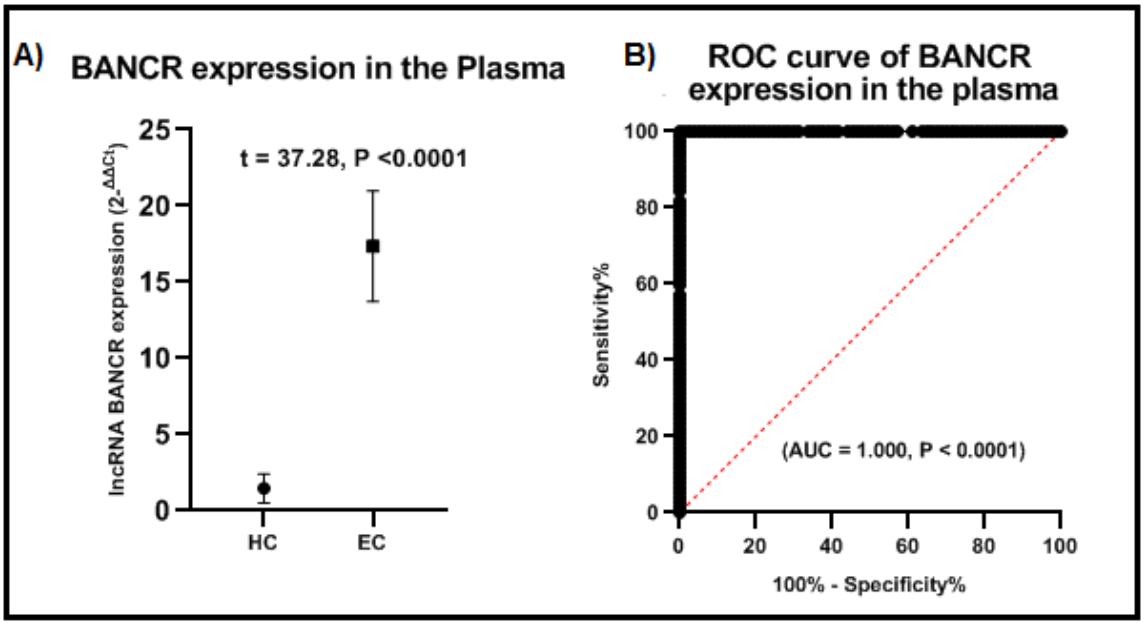

Figure 2: Inc RNA BANCR expression in the plasma

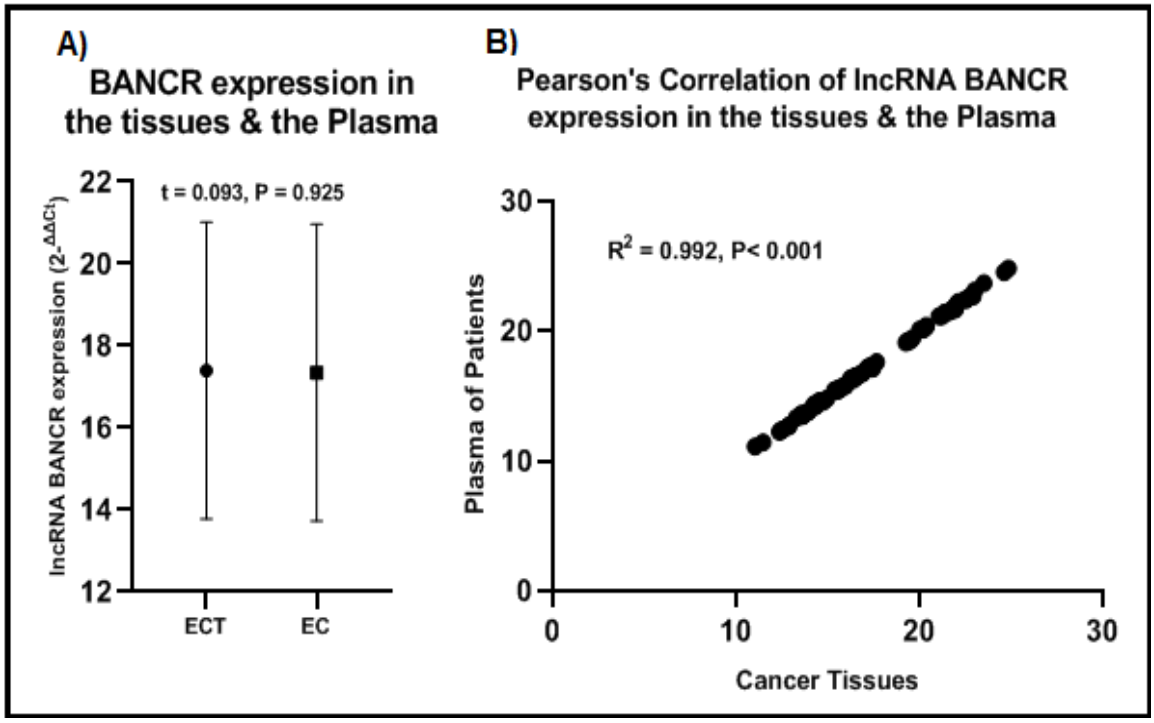

Figure 3: lncRNA BANCR expression in the tissues and the plasma

A) lncRNA BANCR expression levels in both esophageal cancer tissues (ECT) and the plasma of the of patients (EC), Student's t-test = 0.093, P= 0.925.

B) Pearson's correlation curve for lncRNA expression in the plasma of EC versus ECT (R^2 = 0.992, P< 0.001).

LncRNA BANCR expression and clinical and pathological features

We examined the relation between lncRNA BANCR expression in the tumor tissues and the plasma of the patients with their clinical and

pathological features (Table 1). In esophageal cancer tissues, high expression of lncRNA BANCR was significantly related to large tumor size (P< 0.0001), extensive lymph involvement (P< 0.0001), and advanced tumor stage (P< 0.0001). Meanwhile, it was not statistically related to age, sex, histopathological type, or tumor grade.

The same observations were noted when we correlated the lncRNA BANCR expression levels in the plasma of patients with their clinical and pathological parameters (Table 1).

A multivariate multiple regression analysis verified the independent impact of the tissues and the plasma lncRNA BANCR expression (P< 0.001), tumor size (P< 0.001), lymph node involvement (P< 0.001), and clinical stage (P< 0.001) (Table 2).

LncRNA BANCR expression and patients' survival

We sorted the patients in the current study into low and high lncRNA BANCR expression according to the mean ± SD value of its expression. In esophageal cancer tissues, the mean level was 17.4 ± 3.7 and in the plasma of patients 17.37 ± 3.6. The means ± SD in both tissues and plasma divided patients into 20 patients with high lncRNA BANCR expression levels and 57 patients with low expressions. Kaplan–Meier curve showed a short 5-year overall survival in the patients with high expression levels of lncRNA BANCR in their excised tumors or their plasma (Figure 4).

Table 1: Correlation between lncRNA BANCR expression and clinical and pathological features of esophageal cancer

	no.	BANCR expression in tissues			BANCR expression in Plasma		
		Mean	SD	P	Mean	SD	P
Age*							
< 50	25	16.69	3.48	0.236	16.64	3.51	0.24
≥ 50	52	17.74	3.66		17.68	3.66	
Sex*							
Male	48	17.55	3.57	0.63	17.49	3.59	0.65
Female	29	17.14	3.74		17.1	3.72	
Histopathology*							
SCC	54	17.57	3.81	0.53	17.52	3.82	0.51
Adenocar	23	17	3.15		16.93	3.14	
Grade**							
GI	15	17.7	3.03	0.07	17.6	3.04	0.07
GII	17	19.24	3.90		19.2	3.91	
GIII	25	16.9	3.38		16.8	3.35	
GIV	20	16.24	3.66		16.2	3.70	
T**							
T1	15	16	2.81	<0.0001	15.91	2.84	<0.0001
T2	35	15.46	2.59		15.43	2.58	
T3	15	20.09	2.78		20.05	2.80	
T4	12	21.43	2.74		21.34	2.77	
N**							
N0	41	15.17	1.98	<0.0001	15.12	1.98	<0.0001
N1	29	19.75	3.57		19.7	3.59	
N2	7	20.71	2.56		20.63	2.53	
TNM Staging**							
I	31	14.74	1.64	<0.0001	14.69	1.621	<0.0001
II	17	15.32	1.76		15.28	1.779	
III	29	21.45	1.85		21.39	1.867	

Table 2: Multivariate multiple regression analyses of clinical and pathological variables correlated with the prognosis of patients with esophageal carcinoma.

	Plasma	Age	Sex	Pathology	Tumor Grade	T	N	Stage
Best-fit values								
Slope	1	0.018	-0.007	-0.009	-0.064	0.159	0.115	0.201
Std. Error	0.003	0.015	0.016	0.015	0.033	0.025	0.016	0.016
95% CI	0.9935 to 1.007	0.01188 to 0.04753	0.03841 to 0.02355	0.03846 to 0.02000	0.1305 to 0.002810	0.1101 to 0.2083	0.08288 to 0.1478	0.1686 to 0.2335
R^2	0.999	0.019	0.003	0.005	0.046	0.357	0.401	0.670
F	93288	1.429	0.2281	0.3957	3.641	41.67	50.14	152.4
P value	<0.0001	0.2357	0.6343	0.5312	0.0602	<0.0001	<0.0001	<0.0001

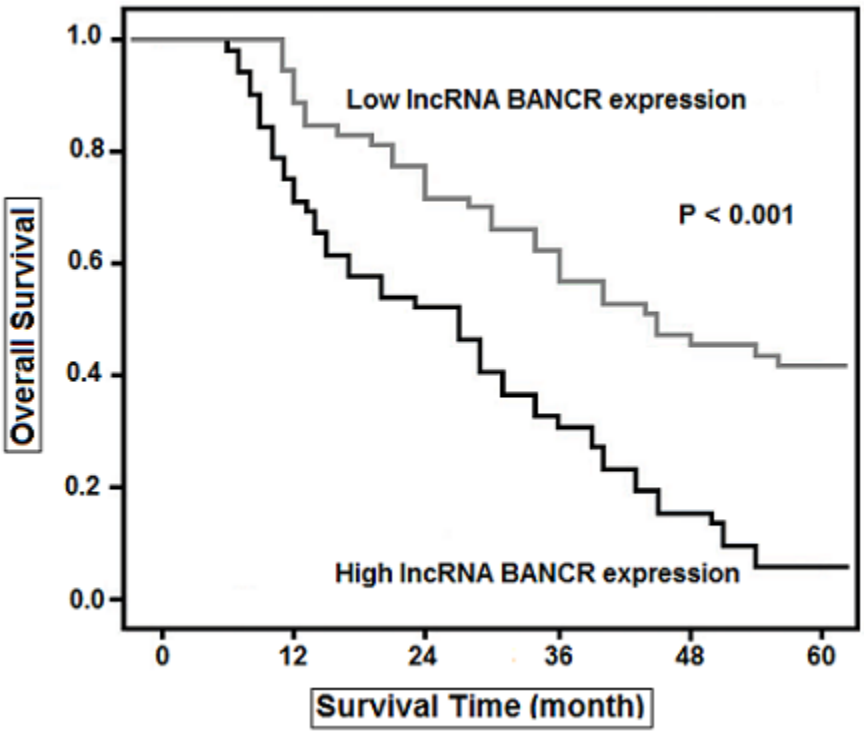

Figure 4: Kaplan Meier curve for the survival of the patients according to lncRNA BANCR expression in esophageal cancer tissues and their plasma (Log-rank test, P< 0.001).

DISCUSSION

Among the most aggressive malignant tumors is esophageal cancer (Li et al., 2013). The absence of successful forms of earlier diagnosis and treatment produces high mortality.

In a variety of malignant tumors, BRAF-activated noncoding RNA (BANCR) identified on chromosome 9 has been described as a tumor suppressor gene in some malignancies and as an oncogene in others, namely the lung cancer, stomach cancer, colon cancer, thyroid cancer, melanoma, hepatocellular carcinoma, and osteosarcoma (Yu et al., 2017). In previous researches, BANCR's roles in cancer are unclear. Some authors concluded that BANCR was highly expressed in cancer tissues and malignant cell lines and that BANCR overexpression stimulated cell migrating by enabling the transition from epithelial to mesenchymal (EMT) (Guo et al., 2014; Wang et al., 2016; Liao et al., 2017). On the opposite, others reported a significant decrease of

BANCR levels in cancer tissues compared with normal tissues and its high expression inhibits cancer cell proliferation, interrupt cell growth, and invasion and increases the rate of apoptosis (Sun et al., 2014; Su et al., 2015; Shi et al.,,2015; Zhang et al., 2018).

These unclear results, in addition to the lack of studies on lncRNA BANCR and its role in esophageal cancer, led us to conduct this study to evaluate its role and its clinical significance ion esophageal cancer.

In the present study, we observed that lncRNA BANCR is highly expressed in esophageal cancer tissues compared to the corresponding normal tissues. Our observation supports the results previously reported in esophageal cancer (Sadeghpour and Ghorbian, 2019), hepatocellular carcinoma (HCC) (Zhou et al.,, 2015), gastric carcinoma (Zhang et al., 2015), oral squamous cell carcinoma (Yao et al., 2019) and malignant melanoma (Li et al., 2014). On the contrary, many studied reported that lncRNA BANCR is significantly down-regulated in a variety of malignant tumors such as colon cancer (Shi et al., 2015), lung cancer (Jiang et al., 2015; Ma et al., 2018), and in urinary bladder carcinoma (He et al., 2016).

We also assessed the plasma levels of lncRNA BANCR in the patients and seventy-seven healthy subjects as control. The plasma levels of lncRNA BANCR was significantly increased in the patients compared to the healthy controls. Our findings support the results of Liu et al., who observed that overexpression of lncRNA BANCR in the plasma of patients with esophageal squamous cell carcinoma (ESCC); also, they observed that lncRNA BANCR level returned to normal after tumor resection (Liu et al., 2016). Our observation was also found by other authors in different cancers such as stomach cancer (Zhang et al., 2017), and HCC (Qin et al., 2017). In our study, the lncRNA BANCR expression both in tissues and in the plasma was nearly equivalent and comparable, with high specificity and sensitivity to esophageal cancer in both tissues and plasma. These findings make it possible to use is as a non-invasive molecular marker for esophageal cancer.

To evaluate the possible use if lncRNA BANCR as a marker for prognosis in esophageal cancer we studied its relation with the prognostic and pathological features. We observed that overexpression of lncRNA BANCR in both tissues and plasma was linked to adverse prognostic and pathological features such as large tumor size, lymph node infiltration, and advanced clinical stage. The results were reported by Liu et al., 2016, in SCCE, who observed that overexpression was related to undifferentiated tumors, lymph node involvement, and advanced TNM stage. lncRNA BANCR over-expression has been associated with the progress of retinoblastoma and positively correlated with tumor size, choroidal invasion, and invasion of the optic nerves (Su et al.,2015). On the other hand, Sun et al., 2014, reported that lowered expression of lncRNA BANCR has been correlated with bigger tumor size, advanced clinical stage, and distant metastases in lung cancer. In bladder cancer, low lncRNA BANCR expression was positively correlated with the advancement of clinical-stage but not related to other clinicopathological features (He et al., 2016).

In the current study, increased levels of lncRNA BANCR in both tissues and plasma were associated with short overall survival supporting the results of other studies in ESCC (Liu et al.,, 2016; Sadeghpour and Ghorbian, 2019), in HCC (Zhou et al., 2015), in melanoma (Ma et al., 2014), and gastric carcinoma (Li et al., 2015). On the contrary, other studies revealed that decreased levels of lncRNA BANCR was linked to short survival in lung cancer (Sun et al.,2014), and in bladder cancer (He et al., 2016).

CONCLUSION

In conclusion, our results showed that lncRNA BANCR acts as a tumor suppressor gene in esophageal cancer, its overexpression in both tissues and plasma was linked to adverse prognostic feature and short overall survival. lncRNA BANCR expression in the plasma can be used as a possible non-invasive molecular marker for prognosis in esophageal cancer..

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEGEMENT

Not applicable

AUTHOR CONTRIBUTIONS

M AlMourgi: performed the research and analyzed the data.

R Alzahrani: analyzed the data, revised the manuscript and scientific conclusion.

N. M. Hawsawi: performed the research, analyzed the data and contributed essential reagents.

W H Elsawy: designed the research study;

performed the research; analyzed the data and wrote the paper.
A F Gharib: designed the research study; performed the research; analyzed the data and wrote the paper.

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