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Clinical Research Article

Expression of Apolipoprotein C-I (Apo C-I) in oral squamous cell carcinoma

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ABSTRACT

Introduction: One of the most common cancers of the oral cavity is oral squamous cell carcinoma (OSCC). Previous studies have provided evidence that apolipoprotein C-I (Apo C-I) has an oncogenic role beyond its classical function. Although it has been investigated in prostate, breast, and lung cancer, there is no information available regarding Apo C-I expression in tumor and pri-tumor tissues of OSCC patients. Thus, the goal of the present study was to unravel the expression of Apo C-I in OSCC and investigate its correlation with the survival and grade of OSCC patients.

Methods: The Apo C-I mRNA level was measured in tumor and pri-tumor tissues of 16 OSCC patients. In addition, the 34 paraffin-embedded tissues of OSCC patients and IHC technique were used to analyze the association of Apo C-I protein with the survival of OSCC patients.

Results: The mRNA (P=0.0386) gene expression of Apo C-I showed a statistically significant difference between tumor and pri-tumor tissues of OSCC patients. It seems that a high protein level of Apo C-I is related with poor survival of OSCC patients (P=0.04). The Apo C-I protein was positively correlated with the tumor site (Pearson r= 0.485, P=0.0036) but not the grade (Pearson r= 0.2295, P=0.1917). Our data showed that high Apo C-I protein levels might be correlated with poor survival of OSCC patients.

Conclusion: Our findings suggest that patients with high protein levels of Apo C-I may have lower survival, making it a potential prognostic factor for OSCC. However, further investigation is necessary to establish this concept.

Keywords:
Apolipoprotein C-I
Oral squamous cell carcinoma
Survival

Introduction

Head and neck cancer is a general term which includes epithelial malignant tumors that occur in the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx. Most of these epithelial malignancies are head and neck squamous cell carcinoma (HNSCC) with a 5-year survival of less than 50% (Argiris et al., 2008; Gharat et al., 2016).

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Oral cancer is ranked as the sixth most common cancer globally. Squamous cell carcinoma (SCC) comprises over 90% of all oral cancers (Feller and Lemmer 2012). The risk factors for these malignancies are tobacco, betel quid, regular alcoholic beverage consumption, and high-risk human papillomavirus (HPV) (Feller and Lemmer 2012; Panarese et al., 2019).

Human apolipoproteins are the protein parts of chylomicron (CM), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL). Apo C-I belongs to the family of apolipoprotein C (Jiang et al., 2021). The synthesis of Apo C-I occurs in the liver and other tissues including the brain, lungs, spleen, and intestines (Ren et al., 2019a). Apo C-I is involved in lipoprotein metabolism (Cui et al., 2020; Ren et al., 2019a). Recently, numerous studies have shown altered expression of apolipoproteins and their association with tumor incidence and progression (Ren et al., 2019b).

The expression of Apo C-I was significantly higher in late-stage lung cancer patients than those with early-stage disease, and the potential of Apo C-I as a prognostic and diagnostic factor for lung cancer has also been proposed (Ko et al., 2014). Additionally, the higher level of Apo C-I is reported in prostate tumor tissues compared to that in healthy tissues (Su et al., 2018). The reported decreased serum level of Apo C-I in advanced stages of ovarian cancer could be considered as a biomarker of both early detection and surveillance of the disease (Huang et al., 2012). Regarding papillary thyroid carcinoma, the potential of Apo C-I as a predictive biomarker in patients with papillary thyroid carcinoma has been proposed (Ren et al., 2019a). Apo C-I is shown to develop the metastasis of clear cell renal cell carcinoma (ccRCC) by activating the EMT pathway and its depletion is reported to relieve this effect (Li et al., 2020b).

Although recent evidence demonstrates the novel function of Apo C-I in tumor progression, no information on the expression and role of Apo C-I in OSCC is available. Our study showed differential Apo C-I expression levels of mRNA and protein between tumor and pri-tumor tissues of OSCC patients which is possibly correlated with their survival. Considering the limited number of patients involved in this work, more investigations would be required to strengthen the prognostic utility of Apo C-I in OSCC.

Material and Methods

Fresh tumor tissue and corresponding adjacent pri-tumor tissue samples were collected from 16 OSCC patients under tumor surgical excision at the Bahman and Shariati hospitals in Tehran, Iran to investigate Apo C-I mRNA expression levels. All fresh samples were stored at -70°C immediately after collection until the investigation. Additionally, the level of Apo C-I protein was compared between tumor and pri-tumor tissues of 34 OSCC Formalin-Fixed Paraffin-Embedded (FFPE) tissues collected from the archives of the Oral and Maxillofacial Department, Tehran University of Medical Sciences. Tumors were classified histologically as Grade I (well-differentiated), Grade II (moderately-differentiated) and Grade III (poorly-differentiated) based on WHO criteria. Table 1 illustrates the patient's demographic and clinicopathological characteristics.

Extraction of RNA and Quantitative RT-PCR

Total RNAs were extracted from OSCC and adjacent pri-tumor tissues using Trizol reagent for RT-qPCR analysis. The purity of the extracted RNA was measured by 260/280 absorbance ratios with NanoDrop device and agarose gel electrophoresis, respectively. The synthesis of complementary DNA was performed on 500 ng of RNA using Primescript RT Reagent Kit (Takara, Otsu, Japan). The RT-qPCR technique was performed using Power SYBR-Green on StepOne Plus RT-PCR system. GAPDH was used as reference gene. Standard curve slope was used to verify the efficiency of primers which ranged from 90% to 100%. Therefore, the $2^{-\Delta\Delta Ct}$ method was used to determine the relative expression levels of Apo C-I. The sequences of primers used in RT-qPCR are summarized in Table 2.

Immunohistochemistry (IHC)

Paraffin-embedded tissues were selected from the archives of the Faculty of Dentistry and approved by a pathologist. Next, 5-micrometer thick sections were cut from the OSCC and adjacent pri-tumor tissues. The sections were deparaffinized by xylene. Rehydration was performed using a descending series of ethanol. The endogenous peroxidase was blocked with 10 min incubation of tissues in hydrogen peroxide. Next, citrate buffer (pH=6) was used to perform the antigen retrieval at 90°C for 15min. Next, the sections were incubated with the Apo C-I primary antibody (ab189866) for 1

Table 1: Clinicpathologic features of OSCC patients

Characteristics	IHC Samples (N=34)	Fresh samples (N=16)
Age mean	57	66
Sex		
Male	22	8
Female	12	8
Grade		
Grade I	19	2
Grade II	12	5
Grade III	3	4
Death		
Yes	19	1
No	15	15
Tumor location		
Oral Cavity	0	0
Tongue	17	6
Floor of the moth	2	0
Lip/ Buccal Mucosa	4	2
Gingiva	1	0
Maxilla	2	0
Mandibula	8	4
Palate	0	2
Man.Vestibule	0	1

Table 2: Forward and reverse primer sequences used for real-time (5' to 3')

Gene	Sequence
GAPDH-F	GCTCAGACACCATGGGGAAG
GAPDH-R	TGTAGTTGAGGTCAATGAAGGGG
APOC1-F	CGGTCCTGGTGGTGGTTCTG
APOC1-R	GTTTGATGCGGCTGATGAGTTCC

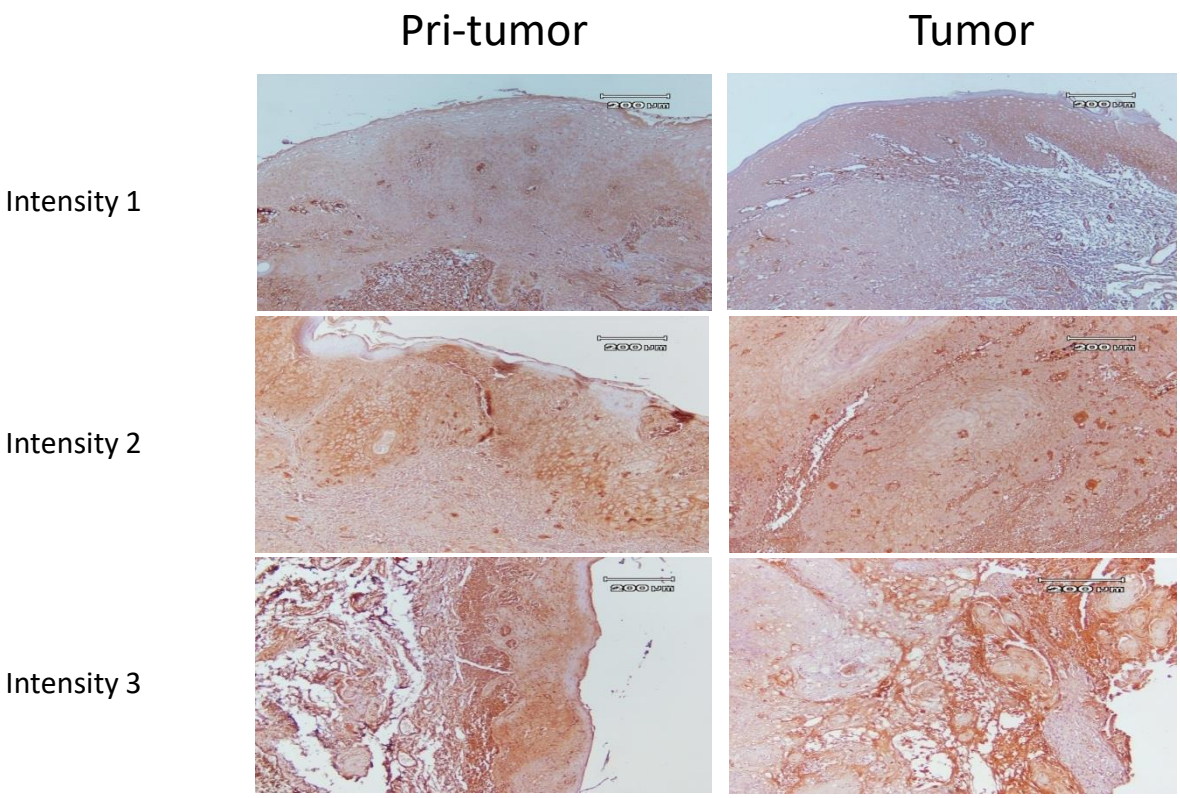

FIGURE 1. Images of tumor and pri-tumor tissue samples of OSCC patients immunostained with Apo C-I showing the intensity scoring from 0 to 3. The scores of signal intensities were assigned for Apo C-I as: negative (0), weak (1), moderate (2) and strong (3) using a light microscope. Original magnification, 400X; Scale bar=200µm

hour at room temperature, washed three times with PBS, were incubated with primary antibody amplifier master for 20 minutes, followed by washing again with PBS. The secondary antibody was added and incubated for 30 minutes at room temperature. After this step and washing with PBS, the signal was amplified using substrate chromogen solution. The sections were counterstained with hematoxylin, dehydrated with serial dilutions of ethanol, and mounted.

Analysis of Immunostained slides

The immunostained sections were examined and quantified by pathologist under light microscope. The score of Apo C-I assigned to each slide is based on the staining intensity and the proportion of positively-cell stained. The data of immunostaining were scored based on the following system: for the score of staining intensity: 0 (negative), 1 (weak), 2 (moderate), 3 (strong) (Fig.1); for staining area scoring: 0 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%) and 4 (76–100%). The total staining score was obtained by multiplication of the staining scoring by the intensity score of the signal (range 0 to 12). An optimal cut-off value was considered as follows: a staining index score of ≥6 was considered as high Apo C-I expression and ≤4 as low Apo C-I expression. According to the low or high expression of Apo C-I, OSCC patients could be divided into four categories, which include i/ $OSCC^{low}$ /$Normal^{low}$ (7 out of 34 patients (20.5%)), ii/ $OSCC^{low}$ /$Normal^{high}$ (11 of 34 patients (32%)), and iii/ $OSCC^{high}$ /$Normal^{low}$ (5 of 34 patients (14%)) and iv/ $OSCC^{high}$ /$Normal^{high}$ (11 of 34 patients (32%)) (Table 3).

Statistical analysis

GraphPad Prism version 6 was applied for data analysis.The data are shown as an average standard deviation (SD). Statistical analysis was done using the paired t-test. Survival analysis was performed using the Kaplan-Meier method and log-rank test. The correlation coefficients were calculated based on Pearson's correlation two-tailed analysis. p-values <0.05 were considered statistically significant in all cases.

Table 3: Comparison of Apo C-I protein expression according to high and low level of Apo C-I total score staining

Total.score	No.	
Low/low	7	(20.5%)
Low/High	11	(32%)
High/Low	5	(14%)
High/High	11	(32%)

PN	Age	Sex	Apo C-I	
			Tumor	Pri-tumor
1	61	F	Low	Low
2	71	M	High	Low
3	45	M	Low	High
4	65	M	High	High
5	42	M	High	Low
6	57	M	High	Low
7	62	F	High	High
8	38	M	Low	Low
9	38	M	Low	High
10	51	M	High	High
11	77	M	Low	Low
12	67	M	Low	High
13	90	F	Low	Low
14	90	F	High	High
15	35	F	High	High
16	56	F	High	Low
17	56	M	High	High
18	43	M	High	High
19	41	F	Low	High
20	46	M	Low	Low
21	75	F	High	Low
22	40	F	Low	High
23	35	F	Low	High
24	65	M	Low	Low
25	75	M	High	High
26	68	M	High	High
27	45	M	Low	High
28	45	M	High	High
29	65	M	Low	Low
30	45	F	Low	High
31	57	F	High	High
32	74	M	Low	High
33	56	M	Low	High
34	76	M	Low	High

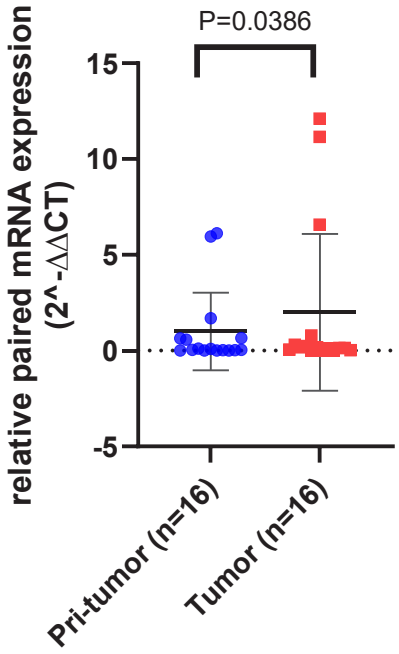

FIGURE 2. Comparison of Apo C-I mRNA level between tumor and pri-tumor tissues of OSCC patients.
mRNA expression of Apo C-I between tumor and peri-tumor tissues of 16 OSCC patients, results normalized to GAPDH housekeeping gene.

Results

Apo C-I mRNA levels in tumor and pri-tumor tissues of OSCC patients

The RT-qPCR data of paired tumor and pri-tumor tissues related to 16 OSCC patients showed statistically significant higher Apo C-I mRNA gene expression levels (P=0.0386) in tumor compared to pri-tumor tissues (Fig.2).

Correlation of Apo C-I expression in tumor tissue with survival of OSCC patients

The Kaplan-Meier curve was used to identify the impact of the Apo C-I protein expression on the patient's survival. We performed a logrank test to find if the survival was significantly different between two groups of patients with high and low expression of Apo C-I. Patients were stratified into two groups of high and low Apo C-I protein expression according to the total Apo C-I score and the defined cut off values. This classification was used to correlate Apo C-I levels with the survival outcomes of OSCC patients. Based on the Apo C-I total staining score, patients with high protein expression level of Apo C-I may have significantly shorter overall-survival compared to those with low level of Apo C-I protein (P=0.040, log-rank test) (Fig.3).

Correlation of tumor location and grade with Apo C-I protein expression

The anatomical locations of OSCC included the oral cavity (0%), tongue (50%), lip/buccal mucosa (11.76%), gingiva/mandibular mucosa (2.94%), mouth floor (5.88%), maxilla (5.88%), mandibula (23.52%), palate (0%), and mandibular vestibule (0%). The correlation between the clinical and pathological features of the patients and tumors including age, gender, tumor site and grade was investigated with different parameters of Apo C-I, using the Pearson's correlation coefficient and associated p-values. Both Apo C-I total scores and intensity score showed positive correlation with tumor site, but Apo C-I staining score did not show significant correlation (Fig.4A, B and C). Interestingly, we found different values of Apo C-I parameters depending on the tumor site. For example, we observed that the Apo C-I intensity score had much lower and higher values in the tongue and Lip/Buccal mucosa, respectively (Fig. S1A). For the Apo C-I total score, we found particularly low values in gingiva and higher values in the Lip/Buccal mucosa (Fig.S1C). Additionally, none of the Apo C-I

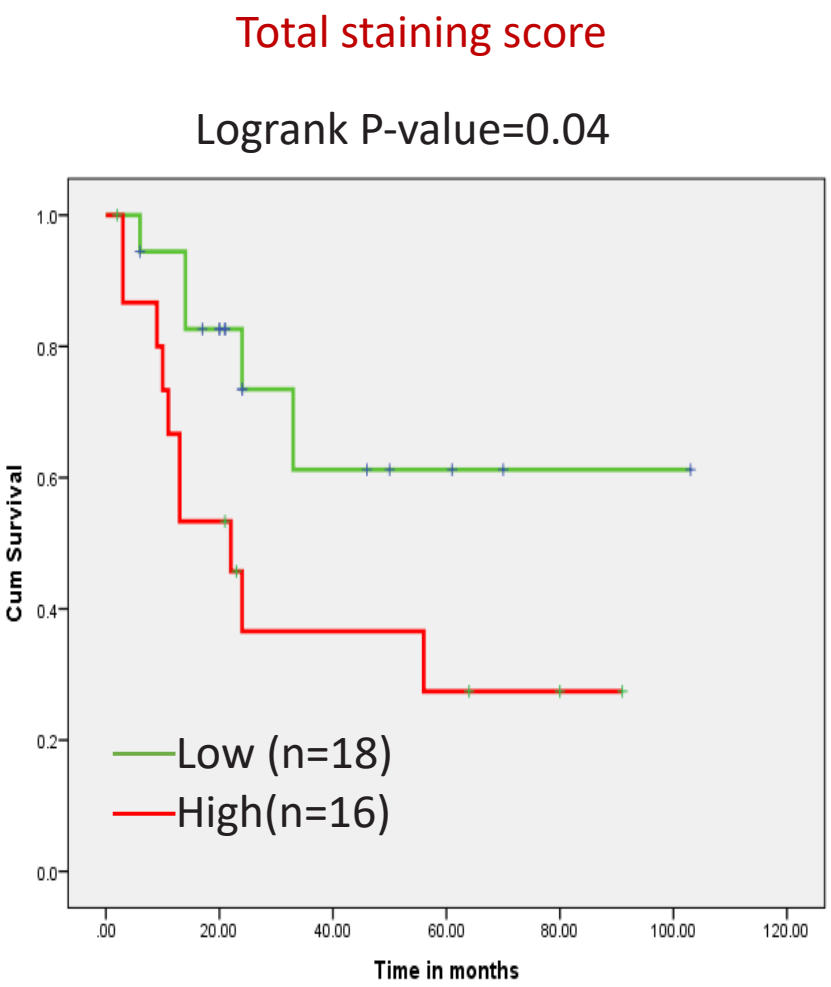

FIGURE 3. Kaplan-Meier survival curves of OSCC patients according to Apo C-I protein.
Patients were stratified to two groups of high and low values based on the Apo C-I total score, the log-rank test analysis showed significant association between total score of Apo C-I with survival of OSCC patients (P-value=0.04).

parameters were correlated with the grade of tumors (Fig.4D, E and F).

Discussion

The most common type of oral cancer is OSCC with dissatisfactory survival rate, which is invasive (Li et al., 2020a). The high-risk and low risk areas for this cancer include the ventrolateral tongue/ floor of the mouth and the palatal mucosa/tongue dorsum, respectively(Thomson et al., 1999). Treatment methods vary based on the primary tumor area and its accessibility. Important treatment methods such as surgery and radiotherapy are effective in 90% and 70% of patients in stage one and stage two, respectively (Argiris et al., 2008). Lipoproteins are particles composed of fat and protein that carry hydrophobic substances in plasma. Lipoproteins are classified based on density into CM, VLDL, LDL and HDL (Dominiczak 2001; Durrington 2003). Lipoproteins are secreted from the intestine and liver and contain special apolipoproteins on their spherical outer surfaces. Apolipoproteins are protein parts of lipoproteins responsible for fat transfer as well as regulation of specific enzyme activities and modulating the removal of plasma lipoproteins through receptor-mediated processes (Halliday et al., 1993). Of the 22 known apolipoproteins, most of them have many critical functions in various mechanisms of cancer (Ren et al., 2019b). For example decreased levels of serum APOA1 have been used as predictive marker for metastasis or poor prognosis in many cancers, including nasopharyngeal carcinoma, colorectal cancer, ovarian cancer, non-small cell lung carcinoma (NSCLC), lymphoma, prostate cancer, and renal cell carcinoma(Luo et al., 2015; Shi et al., 2018). APOB has been shown to regulate the expression

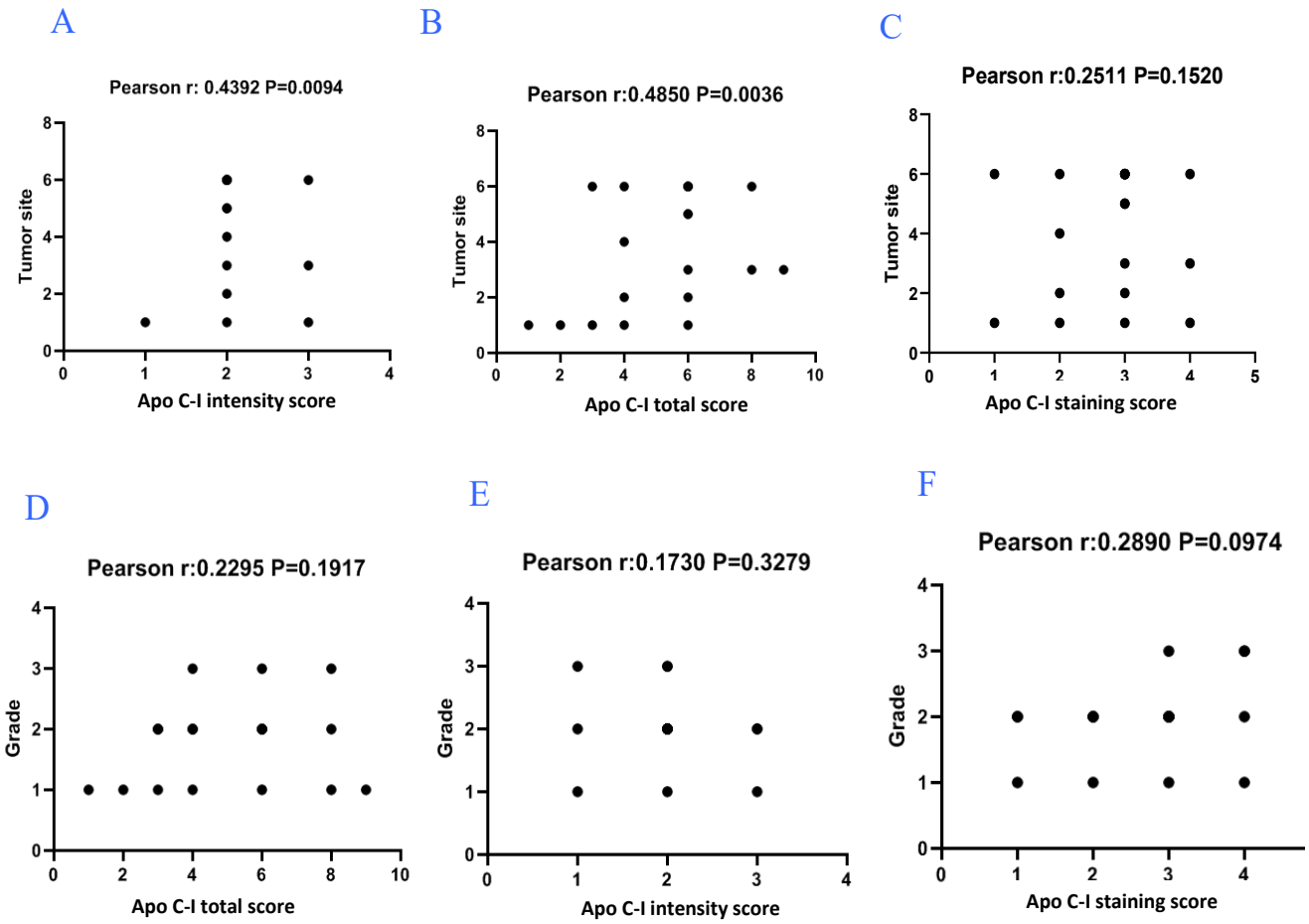

FIGURE 4. The correlation of Apo C-I protein expression with tumor site and grade of OSCC patients.
(A-C) The correlation of Apo C-I intensity, staining and total scores with tumor site. (D-F) The correlation of Apo C-I intensity, staining and total scores with grade of OSCC tumor.

of many genes involved in Hepatocellular carcinoma development and is associated with poor prognosis of Hepatocellular carcinoma patients (Lee et al., 2018). The APOC family is composed of four members, Apo C-I, APOC2, APOC3, and APOC4, that are surface components of CM, VLDL, and HDL (Mahley et al., 1984). Studies have shown that Apo C-I is overexpressed in pancreatic cancer, and an increase in Apo C-I levels in the preoperative serum of patients is considered to reflect an unfavorable prognosis. It has also been observed that suppression of Apo C-I expression prevents the proliferation of pancreatic cancer cells and promote apoptosis of these cells (Takano et al., 2008). Apo C-I overexpression in breast cancer patients has diagnostic utility in distinguishing between triple-negative breast cancer (TNBC) and non-TNBC, therefore it is a potential prognostic factor for TNBC (Sehayek and Eisenberg 1991). Studies have shown that down-expression of Apo C-I significantly suppresses the proliferation of tumor cells, while over-expression of Apo C-I enhances the growth of THP1 and HL60 cells. It has been observed that the expression of Apo C-I mRNA and protein in prostate cancer tissue show a significant enhancement and the serum level of Apo C-I increases in these patients(Klee et al., 2012). Apo C-I serum levels are significantly decreased in colorectal cancer, NSCLC papillary thyroid carcinoma and pediatric nephroblastoma and may be a diagnostic or prognostic marker for these cancers. There is evidence that Apo C-I facilitates tumor development in colorectal cancer via the MAPK signaling pathway (Xue et al., 2012; Yang et al., 2009). Although the role of Apo C-I has been investigated in a variety of cancers, the information on this target in OSCC is limited; hence for the first time, we focused on the mRNA gene expression level of Apo C-I in tumor and pri-tumor tissues of OSCC patients and unraveling the association of Apo C-I protein with OSCC patients' survival. The results of our work on examining the gene expression

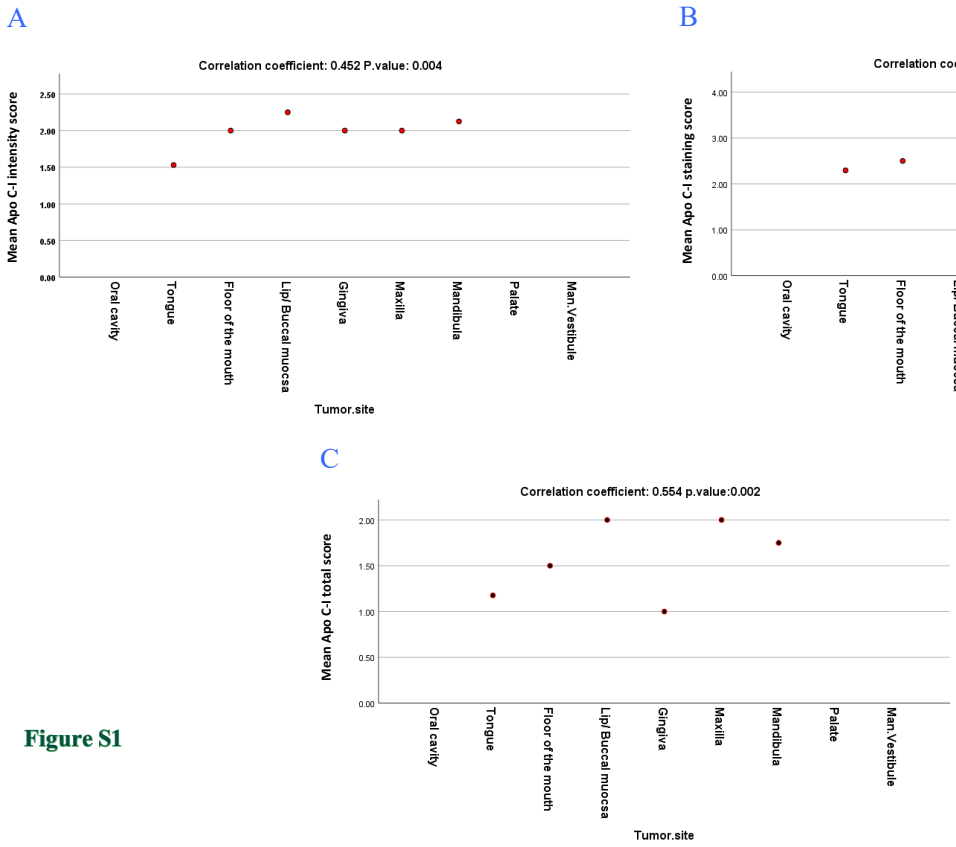

Figure S1

of the Apo C-I mRNA in 16 fresh OSCC and pri-tumor tissues showed a significant difference between tumor and pri-tumor tissues of OSCC patients. In addition, the findings of immunohistochemistry staining on 34 OSCC slides, including both peri-tumor tissues compared to tumor tissue of OSCC patients, showed a high level of Apo C-I protein in peri-tumor tissues. The results from the Kaplan-Meier curve analysis of OSCC tissues indicated that patients with high total scores of Apo C-I are associated with lower chances of survival compared to patients with low total scores of Apo C-I. Also, the results showed that the level of Apo C-I expression is not related to the tumor grade of the patients. Interestingly, we also found that the Apo C-I protein is expressed in the membrane part of cells in the normal tissue, while in the cancer tissue it is also observed in the nucleus in addition to the membrane. Altogether, the observed differential expression of Apo C-I pave the way for future research on potential prognostic utility of Apo C-I for OSCC. Further studies are needed to unravel the mechanism underlying possible Apo C-I association with survival of OSCC patients observed in this study. To understand through which mechanism high level of Apo C-I could result in poor prognosis of OSCC patients, one need to inhibit Apo C-I activity and investigate its effect on tumor growth and metastasis of OSCC in vitro.

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Authors' contributions

AG and ZS participated in the study design. AG supervised the study. KHM performed RT-qPCR and immunohistochemistry. WA helped with the RT-qPCR experiment. AK provided the patient's samples. SD was involved in reading the immunostained slides. KHM and AG performed statistical analysis and wrote the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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