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Identifying SCC Lesions Capable of Spontaneous Regression by Using Immunohistochemistry: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Keratoacanthoma (KA) and squamous cell carcinoma (SCC) are two cutaneous conditions with morphological resemblance, which can complicate the diagnosis in some cases. Using immunohistochemistry staining of biomarkers could be beneficial in resolving this obstacle.

Objectives: We investigated a variety of biomarkers assessed in different studies in order to find the most important and helpful biomarkers for differentiation between SCC and lesions capable of spontaneous regression.

Methods: MEDLINE via PubMed and Google Scholar database were used to identify relevant literature up to 15 June 2022. The aim of our analyses was to determine the capability of biomarkers to distinguish between SCC and lesions capable of spontaneous regression using calculated individual and pooled odds ratios (OR) and 95% confidence intervals (CI) and I^2 tests.

Results: Six potential biomarkers were CD10 with pooled OR= 0.006 (95% CI: 0.001–0.057) and I^2=0%; COX-2 with pooled OR=0.089 (95% CI: 0.029–0.269) and I^2=17.1%; elastic fibers with pooled OR= 6.69 (95% CI: 2.928–15.281) and I^2=0%; IMP-3 with pooled OR=0.145 (95% CI: 0.021–1.001) and I^2=44.5%; P53 with pooled OR=0.371 (95% CI: 0.188– 0.733) and I^2=55.9%; AT1R with OR=0.026 (95% CI: 0.006– 0.107).

Conclusions: We suggest the utilization of the following IHC biomarkers for discrimination between lesions with spontaneous regression such as KA and SCC: CD10, COX-2, and elastic fibers.

Introduction

Cutaneous squamous cell carcinoma is the second most common non-melanoma malignant tumor of the skin, following basal cell carcinoma (BCC), and is also the leading cause of death related to non-melanoma skin cancer. The incidence rate of cutaneous SCC is rising continuously, primarily because of population aging and an increased screening rate [1, 2]. It is characterized by the uncontrolled proliferation of atypical keratinocytes within the epidermis, which should be excised. Apart from population aging, other risk factors are mainly genetic factors, male sex, smoking, immunosuppression, and ultraviolet irradiation, primarily due to sun exposure [3, 4]. Early diagnosis of such lesions is crucial. The diagnosis is based on the appearance, location (sun-exposed), and the patient's medical history. More importantly, the physician's suspicion would lead to more evaluation and eventually to reaching the diagnosis [5]. The gold standard for SCC diagnosis is still to obtain a skin biopsy and histopathologic evaluation[6].

Keratoacanthoma (KA), on the other hand, is considered a premalignant lesion with the potential capacity for transformation into SCC and is, therefore, a precursor of SCC. However, meta-analysis studies have pointed out a 12% probability of the transformation of KA into SCC [7]. Indeed, KA is a spontaneously regressing type of SCC [8]. If not transformed into SCC, KA would regress spontaneously within weeks [9]. Similar to SCC, the gold standard method of diagnosis of lesions capable of spontaneous regression is tissue biopsy and histological findings [7].

It should be mentioned that some studies consider KA, which are lesions capable of spontaneous regression, as a subbranch of SCC [10, 11], and other studies do not consider these two diseases as separate from each other [12]. Although the features of these 2 types of lesions are alike in some aspects, the outcomes diverge. Hence, it is imperative to discriminate between these lesions. Nevertheless, a solid criterion is lacking for this manner [9]. A number of studies have assessed the role of diverse cellular and nuclear markers in the differentiation between these two lesions. Some of these markers have been evaluated in several studies, while other markers have been determined in single studies. In this study, we intended to analyze the effectiveness of these markers in identifying lesions capable of spontaneous regression like KA and SCC.

2. Methods

The present systematic review and meta-analysis was performed based on the PRISMA statement.

2.1 Search Strategy and Screening

To determine research studies that assessed Immunohistochemistry (IHC) biomarkers participating in differentiating between SCC and lesions capable of spontaneous regression, a literature search was conducted using 'MEDLINE via PubMed and Google Scholar database up to 15 June 2022. The following keywords were used in the search: "keratoacanthomas," "KA," "lesions capable of spontaneous regression," "squamous cell carcinoma," "SCC," "differentiation," "diagnoses," "biomarkers," and "IHC." The authors screened the titles, abstracts, and full texts of selected articles to choose the relevant articles.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria based on the full text were: (1) assessing the IHC biomarkers in differentiating between SCC and lesions capable of spontaneous regression; (2) analyzing the IHC biomarkers on subtypes of skin cancers that must contain lesions capable of spontaneous regression and SCC. The exclusion criteria were: (1) publications not in English; (2) non-IHC methods; (3) analysis of other subtypes of skin cancers without containing both SCC and lesions capable of spontaneous regression.

2.3 Data Extraction

Two authors reviewed all the suitable publications. Extracted data were organized into an Excel spreadsheet. The following data were collected from each study: first author's name, publication year, journal, biomarker(s), sample size (total and individual SCC and lesions capable of spontaneous regression), IHC staining positivity of lesions capable of spontaneous regression samples, and the significance of statistical analyses (obtained *P* value).

2.4 Statistical Analysis

R software was used to conduct statistical analyses to compare the odds ratio (OR) with 95% CI of SCC and lesions capable of spontaneous regression. Pooled ORs with 95% CI and I^2 test for heterogeneity were calculated for the biomarkers investigated in at least 2 publications. The consistency of studies was evaluated by the I^2 heterogeneity test, which is interpreted as follows: 0% represents no inconsistency, and 100% represents total heterogeneity. The significance of heterogeneity was considered if the *P* value was <0.1.

3. Results

3.1 Relevant Studies and Flowchart

Among 64 relevant manuscripts, 33 were excluded based on the inclusion and exclusion criteria. Thirty-one relevant publications from 1989 to 2021 were reviewed, and data were extracted for analysis (Table 1). Overall, 43 biomarkers were studied, of which 14/43 were assessed in at least two studies, and 23/43 were investigated once. This selection is shown in Figure 1. The OR and 95% CI of these biomarkers were evaluated. Finally, seven significantly effective biomarkers that could differentiate between SCC and lesions capable of spontaneous regression were selected and are discussed.

3.2 Meta-analysis

The individual and pooled OR and *P* values of 24 single [13-26] and 13 repeated [14, 18-20, 23-25, 27-41] biomarkers are listed in Table 2 and Table 3. The odds of lesions capable of spontaneous regression IHC staining of a specific biomarker, compared with SCC, represent the OR. Calculated infinite OR was excluded due to insensible analysis. However, in order to include studies with zero calculated OR, Peto's method was used. These selected biomarkers' capability to differentiate between SCC and lesions capable of spontaneous regression was demonstrated by statistically significant OR with 95% CI. AT1R was the single IHC biomarker, and CD-10, COX-2, elastic fibers, IMP-3, and P53 were repeated IHC biomarkers.

3.3 Cluster of Differentiation 10

The cluster of differentiation (CD) 10 is a cell surface ectoenzyme marker used for the diagnosis and differentiation of cancers [42]. There is a correlation between tumor cell proliferation and the number of CD10+ dermal tumor-associated macrophages (TAM) and epidermal Langerhans cells (LC) in the development of epidermal tumors. Indeed, these components are important cellular elements of the tumor microenvironment. It has been reported that the number of LCs in SCC and malignant melanoma is lower than in normal skin. It is assumed that the induction of CD10+ stromal cells may be associated with the infiltration of TAMs and loss of LCs. Therefore, $CD10^+$ stromal cell induction, increased TAMs, and decreased LCs are related to each other, and these 3 items correlate with the rate of tumor proliferation [27]. Two similar studies were evaluated to determine whether CD-10 can serve as a differentiating biomarker for SCC and lesions capable of spontaneous regression [27, 34]. Together, these two studies had 60 samples, of which only four samples of lesions capable of spontaneous regression were positive for CD-10 IHC staining compared with all positive SCC samples (33 samples). The pooled OR was calculated at 0.006 (95% CI: 0.001–0.057) for lesions capable of spontaneous regression compared to SCC, meaning that the tendency of SCC lesions to have positive IHC staining for CD-10 was 166.7 times higher in comparison with lesions capable of spontaneous regression. There was also no statistically significant heterogeneity between studies (I^2=0%).

3.4 Cyclooxygenase 2

Cyclooxygenase 2 (COX2) is a key enzyme that produces prostaglandins involved in the inflammatory process [43]. A total of two studies were reviewed for this biomarker [23, 29]. The pooled OR of these studies (lesions capable of spontaneous regression compared with SCC) was calculated at 0.089 (95% CI: 0.029–0.269). These two studies did not have heterogeneity since I^2=17.1%. For this reason, the OR of COX-2 IHC staining for SCC compared with lesions capable of spontaneous regression was 11.2.

3.5 Elastic Fiber

Elastic fibers are extracellular components that exist in many tissues, such as the skin, and are important for the skin's physiological processes [44]. Data extracted from two studies [30, 45] were assessed for this biomarker, revealing a calculated pooled OR of 6.69 (95% CI: 2.928–15.281) for lesions capable of spontaneous regression compared with SCC. Of 118 total samples, 47 were positive for lesions capable of spontaneous regression, while 15 were positive for SCC. The calculated I^2 was 0%, meaning that the studies were consistent with one another.

Table 1. Characteristics of included studies.

Author	Year	Total sample size	Mean Age (KA)	Mean Age (SCC)	Biomarkers
Stephenson et al. [24]	1992	88			P53/nm23
Urano et al. [33]	1992	27			P53
Kerschmann et al. [35]	1994	50			P53
Watanabe et al. [77]	2015	40			P53/ Ki-67/ CD-34/ CD-105
Cain et al. [36]	1995	24			P53/ PCNA
Sakiz et al.[20]	2009	29			P53/P63
Vasiljevic et al. [14]	2009	89			P53/ Ki-67/ P16/ Bcl-xL/ Bcl-x/ CD-3/ CD-20/ CD68/ NFκB/ IκBα/ STAT3/ pRb/ P21/ Survivin/ BAK/ FLK-1/ Cyld/ TRAP-1/ Caspase-3
Batinac et al. [37]	2006	120	68.5	76.3	P53/ Ki-67/BAK/ Bcl-2/
Ribeiro et al. [18]	2008	108			P53/PCNA/Bcl-2/MIB-1 /Caspase-3
Khodaeiani et al. [38]	2013	18			p53/ ki-67/
Bedir et al. [25]	2016	70	71	74	p53/ki-67/p16/p21/p27
Putti et al. [23]	2004	41			P53/COX-2/Telomerase
Leblebici et al. [84]	2017	51	63.7	74.6	Ki-67/ Cytokeratin-17
Takahara et al. [27]	2009	30			Ki-67/CD-10/CD-68 /CD-1a
Soddu et al. [32]	2013	67	69.5	76.1	IMP-3
Kanzaki et al. [31]	2016	23	61.7	78.4	IMP3
Hua et al. [29]	2015	55			COX-2
Markey et al. [19]	1990	15			B2M/ MHC II
Graham et al. [39]	1987	91	62.4	69.7	B2M
Jordan et al. [45]	1991	100	66.2	74	Elastic Fiber
Philips et al. [30]	1993	18			Elastic Fiber/ PCNA
Kaabipour et al. [40]	2006	48	66.3	74.5	P16
Tan et al. [26]	2009	55			Bcl-x
Tanikawa et al. [41]	1992	12			P21
Cabibi et al. [17]	2016	30	62	74	HSP60/ CD-1a
Gambichler et al. [22]	2017	47			PD-L1
Krunic et al. [15]	1998	36			Dsg1 and Dsg2
Takeda et al. [13]	2001	72			AT1R
Jia et al. [16]	2021	45	63	63.6	HSP-105
Tran et al. [21]	2000	55			OSM
Gouda et al. [28]	2014	35			P53/ Ki-67/CD10

3.6 Insulin-like Growth Factor 2 mRNA-binding Protein

The insulin-like growth factor 2 (IGF-2) mRNA-binding protein (IMP) is a protein family that binds to IGF-2 mRNA and regulates its transcription [46]. Previous studies evaluating IMP-3 as a biomarker for differentiating between SCC and lesions capable of spontaneous regression were conducted by Soddu et al. and by Kanzaki et al. [31, 32]. In the former study, 9/34 were positive for lesions capable of spontaneous regression compared to 19/33 for SCC. In the latter study, all eight samples of lesions capable of spontaneous regression were negative, while 10/15 of SCC samples were positive for IHC staining of IMP-3. The pooled OR of these two studies was 0.145 (95% CI: 0.021–1.001), which is defined as a 6.9 times greater tendency of SCC lesions for IMP-3-positive staining compared with lesions capable of

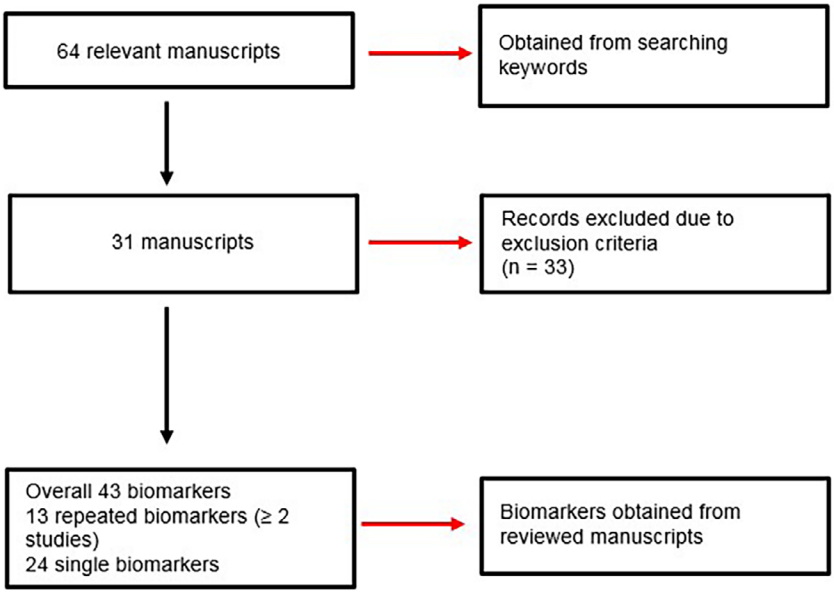

Figure 1. Prisma flow diagram illustrating the selection of articles.

Table 2. Results of 13 biomarkers with repeated studies.

Biomarkers	Pooled OR (KA/SCC)	95% CI	I^2	*P* value of pooled OR (calculated)
CD10	**0.006**	0.001 – 0.057	0%	<0.0001
COX-2	**0.089**	0.029 – 0.269	17.1%	<0.0001
Elastic Fiber	**6.689**	2.928 – 15.281	0%	<0.0001
P53	**0.371**	0.188 – 0.733	55.9%	0.004
IMP-3	**0.145**	0.021 – 1.001	44.5%	0.05
Ki-67	OR=0.143	0.026 – 0.774	-	0.024
B2M	18.13	0.251 – 1309.386	77.6%	0.184
PCNA	2.032	0.902 – 4.579	0%	0.087
P16	1.176	0.483 – 2.866	-	-
P21	OR=1.75	0.512 – 5.978	-	0.372
BAK	4.90	0.252 – 95.68	59.9%	0.294
BCL-2	OR=0.689	0.323 – 1.472	-	0.337
Caspase 3	2.562	0.032 – 206.1	97.1%	0.674

spontaneous regression. Although the calculated I^2 test was 44.5%, this heterogeneity was not statistically significant.

3.7 P53

P53 is a tumor suppressant transcription factor that, upon activation, causes downstream events that suppress cell cycle and proliferation [47]. For a careful assessment of the capability of P53 for the differentiation of SCC and lesions capable of spontaneous regression, a total of 12 studies were reviewed [14, 18, 20, 23, 25, 33-38, 48]. There were 730 samples (lesions capable of spontaneous regression=354, SCC=376) with a calculated pooled OR (lesions capable of spontaneous regression compared with SCC) of 0.371 (95% CI: 0.188–0.733). The I^2 percentage of heterogeneity was 55.9%, which was statistically significant. Individual and pooled ORs are shown in Figure 2.

3.8 Angiotensin II Receptor Type 1

Angiotensin II receptor type 1 (AT1R) is one of the two types of angiotensin II receptors, which, after activation, is responsible for the homeostasis of blood pressure and body electrolytes, alongside other effects. Among the other effects of

Table 3. Results of 24 biomarkers with single study.

Biomarker	OR (KA/SCC)	95% CI	Obtained *P* value from studies	Calculated *P* value of OR
AT1R	**0.026**	**0.006 – 0.107**	-	**<0.0001**
CD-20	Infinite	-	N/S	-
CD-3	Infinite	-	N/S	-
CD-68	0.981	0.309 – 3.109	N/S	0.974
Cyld	Infinite	-	N/S	-
Dsg 1 & 2	10.714	0.559 – 205.382	-	0.116
FLK-1	Infinite	-	N/S	-
HSP-105	0.733	0.138 – 3.88	-	0.716
HSP-60	8.81	0.385 – 201.383	<0.05	0.173
IκBα	0.264	0.014 – 5.078	N/S	0.377
MHC-II	1.2	0.121 – 11.865	-	0.876
MIB-1	0.074	0.004 – 1.348	<0.05	0.079
NF-κB	Infinite	-	N/S	-
OSM	3.529	0.947 – 13.153	0.001	0.06
P63	Infinite	-	-	-
PD-L1	1.357	0.387 – 4.759	-	0.633
STAT-3	0.49	0.023 – 10.571	N/S	0.649
Survivin	Infinite	-	N/S	-
TRAP-1	0.708	0.137 – 3.666	N/S	0.681
Telomerase	0.448	0.017 – 11.659	0.001	0.629
nm-23	Infinite	-	0.189	-
P-27	Infinite	-	0.744	-
pRb	Infinite	-	N/S	-
Bcl-xl	1.029	0.29 – 3.642	<0.001	0.965

AT1R activation are cell growth and migration [49]. In the study by Takeda et al. [13], AT1R was evaluated in 72 samples (22 lesions capable of spontaneous regression samples compared with 50 SCC samples): 5/22 samples of lesions capable of spontaneous regression were positive on AT1R IHC staining, while 46/50 SCC samples had the same result (calculated *P*<0.0001). The calculated OR (lesions capable of spontaneous regression in comparison with SCC) was 0.026 (95% CI: 0.006–0.107), meaning that the SCC lesions were 38.4 times more likely to express AT1R than lesions capable of spontaneous regression.

4. Discussion

Mentioned above is that the gold standard for the diagnosis of both SCC and lesions capable of spontaneous regression is biopsy sampling and histopathological evaluation, and that all of the evaluated lesion samples in the studies that we reviewed for IHC staining of various biomarkers had been previously diagnosed for SCC or as lesions capable of spontaneous regression. Therefore, it is worth mentioning that IHC staining of these diverse biomarkers is beneficial where a net diagnosis between these two lesions, with the capability of spontaneous regression, is complex and challenging [9, 50]. More importantly, it should be considered that this diversity in biomarkers indicates that the diagnosis based on one biomarker is insensible. Hence, a combination of these biomarkers should be utilized to differentiate between SCC and lesions capable of spontaneous regression. For this reason, we investigated a variety of biomarkers assessed in different studies to identify the most significant and useful biomarkers for this differentiation. Of all 43 biomarkers, after statistical analyses of the extracted data, six biomarkers had significantly more probability of distinguishing between the two entities. Five out of six biomarkers were assessed in two or more studies, including CD-10, COX-2, elastic fibers, IMP-3, and P53. The other biomarker, AT1R, was evaluated in only one study. Other biomarkers that were investigated repeatedly were Ki-67, B2M, PCNA, P16, P21, BAK, Bcl-2, Caspase-3, and CD-1a. Repeated biomarkers are highly important since they give us information across the studies, and their analysis results are more reliable. For a complete

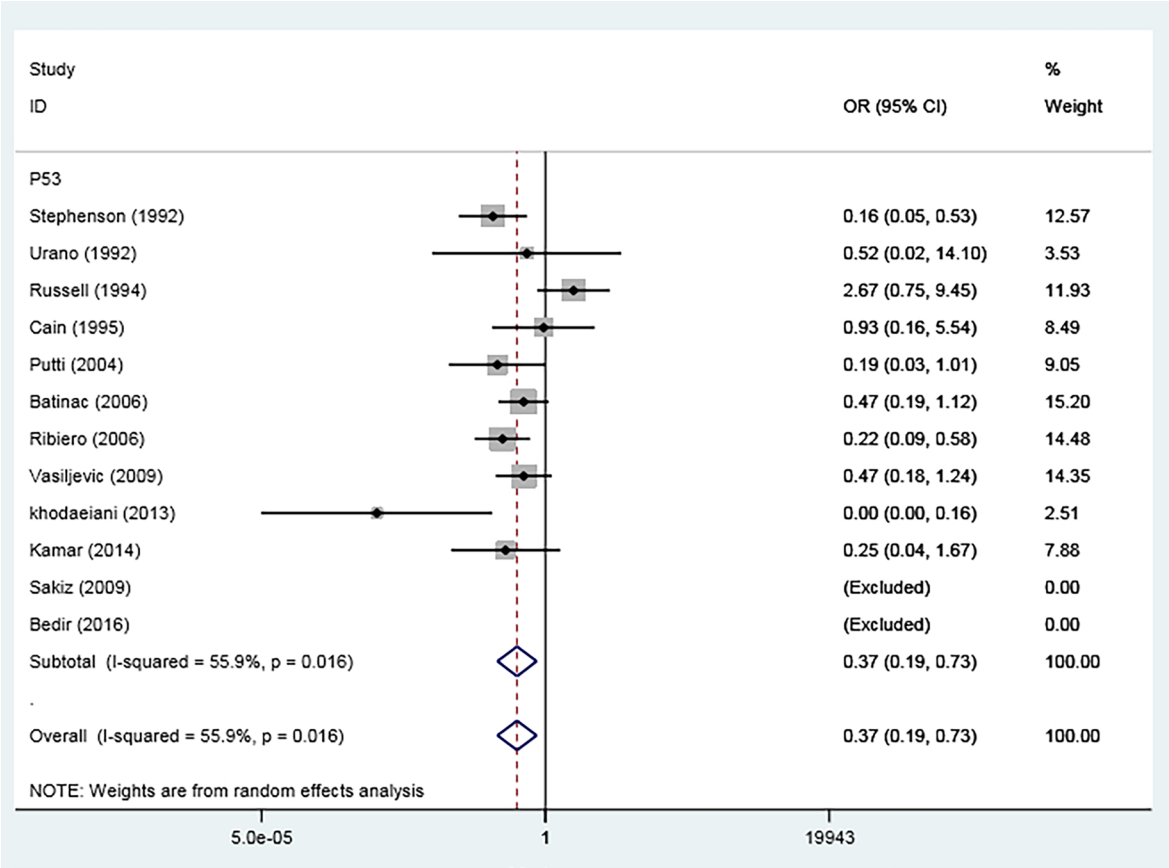

Figure 2. Forest plot for P53.

evaluation, the consistency of these studies was assessed by statistical analysis.

The reviewed studies for CD10 had a similar trend of OR for comparison of SCC and lesions capable of spontaneous regression. Therefore, the results of the statistical significance of this biomarker for differentiation are reliable. CD10 is expressed in the epithelial cells of various tissues and has been widely used in diagnosing different skin cancers, including SCC, BCC, and melanoma [51]. The overexpression of CD10 in skin cancer cells promotes rapid tumor progression and proliferation, leading to a higher grade and a larger tumor size [52-54].

Following the analysis for CD10, the pooled OR was calculated at 0.006 (95% CI: 0.001–0.057) for lesions capable of spontaneous regression compared to SCC. For this reason, CD10 can distinguish between SCC and lesions capable of spontaneous regression, since SCC lesions are 166.7 times more likely to be positive for the IHC of this biomarker. Therefore, SCC lesions are biologically more progressive, with a higher proliferation rate, than lesions capable of spontaneous regression [55]. All reviewed studies had the same OR calculation equal to 0.006. Although the number of studies was limited, the combined total sample size of these studies was acceptable. Furthermore, there was no significant heterogeneity between studies, as I^2 = 0%. Taken together, CD10 can be used as an applicable biomarker to differentiate between these lesions.

Another biomarker is COX-2, which is expressed in skin lesions and through the production of prostaglandins[56]; it is involved in the initiation, invasion, and angiogenesis of tumors and also participates in the suppression of the immune system [57, 58]. UV exposure can induce COX-2 expression, leading to skin malignancies [59, 60]. COX-2 has been demonstrated to be effective in the differentiation between benign and malignant skin lesions [59, 61].

Two studies were reviewed to assess the capability of COX-2 to differentiate between SCC and lesions capable of spontaneous regression. These studies were consistent since the calculated I^2=17.1 % was not significant. Moreover, the trend of OR of these studies was similar. In this study, we demonstrate that COX-2 IHC positivity was 11.2 times more positive for SCC compared to lesions capable of spontaneous regression since the calculated pooled OR was 0.089 (95% CI: 0.029–0.269). According to these results, we can conclude that SCC has a more progressive and invasive behavior compared to lesions capable of spontaneous regression. Taken together, with a considerable sample size, we can indicate COX-2 as an acceptable biomarker for the differentiation between SCC and lesions capable of spontaneous regression.

Elastic fibers are components of dermal connective tissue that maintain the elasticity of the skin. They have considerable distinguishing capabilities between malignancies. Loss of these fibers more often occurs in malignant tumors than in benign lesions [62-64]. The calculated pooled OR, comparing lesions capable of spontaneous regression with SCC, was 6.69 (95% CI: 2.928–5.281) with I^2=0%. Considering the total sample size of these studies, which was 118, and no significant heterogeneity, the results are reliable. The tendency of OR for these two studies was consistent (6.167 and 13.333), confirming the reliability of the results.

The other biomarker is IMP-3. The members of the IMP family are IMP-1, IMP-2, and IMP-3, which bind to the transcript of IGF-2 mRNA [65]. Particularly, the overexpression of IMP-3 has been detected in several malignant cancers [65-70]. Also, the role of this protein has been investigated as a biomarker to differentiate between benign and malignant lesions, including melanoma [71] and SCC [72]. Furthermore, IMP-3 increases the migration of the malignant cells and leads to the invasiveness of the tumor [73]. For this reason, as it is likely that IMP-3 can differentiate between SCC and lesions capable of spontaneous regression, it was evaluated in this manner.

In our study, two studies were reviewed for the assessment of IMP-3 IHC staining. These studies were not significantly heterogeneous; however, the calculated I^2 was 44.5%, which is high compared to other biomarkers. Therefore, the results should be considered more cautiously. The pooled OR was 0.145 (95% CI: 0.021–1.001), with individual ORs equal to 0.265 and 0.031. This means that SCC lesions' biological behavior is more invasive than that of lesions capable of spontaneous regression. Although this pooled OR was considered statistically significant, IMP-3 was 3.9 times more likely to be positive for SCC in the Soddu et al. study [32], while in the Kanzaki et al. study [31], it was 32.2 times more likely to be positive for SCC. This suggests the diversity between the results of these two studies. In other words, IMP-3 should be taken into consideration for the differentiation between SCC and lesions capable of spontaneous regression, but more cautiously and in addition to other biomarkers.

P53 protein is one of the most studied tumor suppressant proteins recognized to date. It is capable of regressing and inhibiting tumors, and the development of many tumors may occur with the mutation of the P53 gene [47]. As discussed in other studies, skin cells with previously mutated P53 genes can develop skin lesions after exposure to the sun [74]. It would seem that P53 is a good biomarker for differentiating between malignant tumors and other lesions, especially in the skin, as other studies have investigated in the past and recently [75, 76].

The highest number of studies in our study were reviewed for this biomarker. Among these 12 studies [14, 18, 20, 23, 25, 28, 35-38, 48, 77, 78], two were excluded due to the calculation of OR since the results were calculated as infinite. Of the remaining ten studies, the trend of OR was towards lesions capable of spontaneous regression, while for other studies, this trend was towards SCC. The calculated OR of that single study was 2.67. Considering the weight of the study (11.93%) compared with other studies, this calculated OR could be ignored. The pooled OR comparing the IHC positivity of lesions capable of spontaneous regression and SCC for P53 was 0.371, and it was statistically significant. In other words, SCC would express P53 3.69 times more than lesions capable of spontaneous regression. The reviewed studies were inconsistent since I^2= 55.9%, which was statistically significant. However, this heterogeneity of the studies could be considered moderate. This indicates that P53 could distinguish between SCC and lesions capable of spontaneous regression when used as a biomarker, but care should be taken so that it is not assessed without other biomarkers.

Although the activation of AT1R has homeostatic effects, studies suggest its role and expression in different types of malignancies [79]. Also, a number of studies have investigated its expression on cancerous cells, revealing AT1R's role in tumor genesis [80]. Consistent with this implication, several treatment approaches were utilized for the management of a number of malignancies, and the results were promising [81, 82]. Moreover, IHC staining of this receptor was evaluated in previous studies for skin lesions, which suggests a high probability of its differentiation capability between skin lesions [83]. AT1R was investigated in one study, by Takeda et al. [13]. SCC significantly expressed AT1R compared with lesions capable of spontaneous regression, with OR (lesions capable of spontaneous regression compared with SCC) of 0.026 (95% CI: 0.006–0.107).

Ki-67, aside from the biomarkers discussed above, had a significant OR in our analyses as well. This biomarker was investigated in six studies [14, 25, 34, 37, 38, 84], five of which were excluded during the analyses due to infinite calculated ORs, which were insensible. The OR of the remaining study was 0.143, indicating a probability of IHC positivity for Ki-6 comparing lesions capable of spontaneous regression with SCC, which was significant. However, when we assessed the excluded studies, all SCC and lesions capable of spontaneous regression samples for each study were entirely positive. This implies that Ki-67 may not be an acceptable biomarker for the differentiation between SCC and lesions capable of spontaneous regression.

Some of the evaluated biomarkers had a high calculated OR compared with other biomarkers, although they were not statistically significant. These biomarkers were B2M, BAK, Dsg1 &2, HSP60, and MIB-1, and their calculated ORs were 18.1, 4.9, 10.7, 8.81, and 0.074, respectively.

Therefore, these biomarkers could be potentially evaluated in future studies for this purpose.

The limitation of our study may be the high number of investigated biomarkers among the small number of studies for each biomarker. Also, there was heterogeneity in the type of reference standard of the studies we reviewed; because the reference standard of the studies was different from one another, and since the number of our studies was not enough, we could not group the studies that were similar in terms of the standard reference into a subgroup or exclude some of them. Therefore, heterogeneity may be seen in the results that was explained above; for future studies, it is therefore suggested to consider studies that have a similar standard reference (such as hematoxylin). In addition, the range of the marker's cutoff for positivity or negativity was also the same as above. Of course, it should be mentioned that the cutoff of our studies was almost the same, and there were no statistically significant differences.

5. Conclusion

In summary, the results of our study show that a number of biomarkers, including CD10, COX-2, and elastic fibers, have a high capability of differentiating between SCC lesions and lesions with the capability of spontaneous regression, such as KA, in cases with a difficult diagnosis. IMP-3, P53, and AT1R could also be utilized in this manner; however, more investigation is required. The presence of these biomarkers was investigated through IHC staining and can be used in the clinical approach to SCC and KA lesions.

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