Intraoral Pigmented Low-Grade Adenocarcinoma, Not Otherwise Specified: Case Report and Immunohistochemical Study

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Abstract

Salivary adenocarcinoma, not otherwise specified (AdCaNOS) is a rare malignant tumor with potential diagnostic challenge, which mainly affects the parotid glands; however, the minor salivary glands can also be involved by AdCaNOS. This paper reports a case of a 45-year-old Afro-descendant woman complaining of a slow-growing mass with 6 months of evolution in the left superior vestibular fornix. Microscopic examination revealed an infiltrative epithelial neoplasm composed of predominantly solid growth pattern, arranged in a lobular configuration, admixed with glandular or ductal structures. Perineural invasion was evident. The tumor cells were polygonal or oval showing focally mild nuclear pleomorphism, and eosinophilic or clear cytoplasm. Notably, some areas exhibited intracytoplasmic pigment granules mainly in non-luminal cells, as well as sebaceous-like cells, discrete hyaline material deposition and foci of infiltration of residual salivary gland parenchyma. Tumor cells were negative for PAS, mucicarmine and Alcian blue stains. By immunohistochemistry, the tumor cells were diffuse and strongly positive for pan-cytokeratin (CK) AE1/AE3, 34betaE12 CK, vimentin, p63 and S100. CK7 and EMA strongly highlighted the ductal structures. Solid areas also showed diffuse and moderate expression of CD56. Podoplanin (D2-40), GFAP and Calponin, followed by DOG-1, were focally positive; whereas CK20, α -SMA, h-Caldesmon, CD57, ERBB2/HER2 and p53 were negative. Ki-67 was <2%. Consecutive serial tissue sections using CD57 confirmed the perineural invasion. Positivity for HMB-45 and MART-1/Melan-A, as well as Fontana-Masson stain (and potassium permanganate bleaching-sensitive), identified the pigment granules as melanin. To the best of our knowledge, this is the first case of intraoral low-grade AdCaNOS with intracytoplasmic melanin granules.

Keywords Adenocarcinoma, not otherwise specified · Salivary gland neoplasms · Pigmentation · Melanin · Oral cavity · Immunohistochemistry

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Introduction

According to the head and neck tumors classification based on the World Health Organization (WHO), there are 20 types of malignant tumors and 11 types of benign tumors from salivary gland origin [1]. Adenocarcinoma, not otherwise specified (AdCaNOS) is a rare entity with potential diagnostic challenge, which requires recognition of its histopathological features and the exclusion of more common salivary gland tumors by detailed morphological and immunophenotypical studies [2]. In fact, overall, the histopathological features of AdCaNOS do not meet the established criteria for other tumor types [2].

The occurrence of AdCaNOS is higher in the parotid glands, followed by minor salivary glands of the palate [1, 3]. By microscopy, AdCaNOS can present several architectural and cellular patterns. The neoplastic epithelium may be glandular, papillary, cystic, cribriform, solid, lobular, nested or cords. Morphological analysis of tumor cells demonstrates several types, such as cuboidal, columnar, polygonal or oval. Furthermore, other cellular types of AdCaNOS have been described, such as oncocytoid, clear, melanoma-like, mucinous, sebaceous and plasmacytoid cells. A single tumor can comprise more than one histopathological pattern. AdCaNOS are classified as low-, intermediate- or high-grade according to the nuclear morphology, pleomorphism, hyperchromatism, necrosis, mitotic index, ill-demarcated borders and infiltrative nature, mainly identified in high-grade lesions [4].

The prevalence of AdCaNOS is variable in the literature, ranging from 1.2 to 19.0% of the malignant salivary gland tumors [2, 5, 6]. Surgery is the treatment of choice; however, other modalities such as radiotherapy and/or chemotherapy can also be considered [2]. The prognosis is dependent on the tumor grade, tumor stage and anatomical location [1]. However, information on metastasis is scarce. Interestingly, one case of AdCaNOS presented multiple metastases and the patient was maintained on chemotherapy with trastuzumab [7]. Nevertheless, reports about AdCaNOS are scarce in the literature, thus, it is imperative that the various histopathological aspects of the AdCaNOS are known, so that its diagnosis is facilitated, avoiding misdiagnosis.

Pigmented salivary gland tumors are unusual. A review of English literature revealed several melanin-pigmented salivary gland tumors, including 18 Wartin's tumor [8], 5 mucoepidermoid carcinoma (MEC) [9–13], 2 adenoid cystic carcinoma (AdCC) [14, 15] and 1 pleomorphic adenoma (PA) [16]. Melanocyte-like cells in the tumor stroma were observed in all cases, whereas some cases also presented pigment granules within tumor cells [10–12, 15, 16] (Table 1). Moreover, 1 PA [17] with lipofuscin

pigmentation has been also reported. The prognostic significance of these findings is not described.

In the current study, we report a rare case of a pigmented low-grade AdCaNOS affecting the upper buccal fornix, which presented diagnostic difficulties. Moreover, we present the histochemical and immunohistochemical findings, emphasizing their differential diagnosis.

Case Report

A 45-year-old Afro-descendant woman sought care at the Oral and Maxillofacial Surgery Department of the School of Dentistry of Ribeirão Preto complaining of slow-growing mass on the left upper buccal fornix with 6 months of evolution. Intraoral examination revealed a nodular and pedunculated lesion with smooth surface, reddish colored and elastic consistency. The panoramic radiography did not show alterations. The initial clinical diagnosis favored a benign mesenchymal neoplasm. The whole lesion was removed under local anesthesia and the material was sent for histopathological analysis. Microscopic examination revealed an infiltrative epithelial tumor, predominantly solid, showing a lobular configuration admixed with several glandular or ductal structures (Fig. 1a, b). The tumor cells were polygonal or oval, showing focally mild nuclear pleomorphism, and eosinophilic or clear cytoplasm. Moreover, oncocytoid cells, sebaceous-like cells and discrete hyaline material deposition (Fig. 1c, d), as well as foci of perineural invasion (Fig. 1e) and normal-appearing salivary gland ducts surrounded by tumor cells were observed (Fig. 1f). Some areas exhibited intracytoplasmic pigment granules mainly in the cytoplasm of the cells forming cords or nests. By histochemistry, periodic-acid Schiff (PAS), mucicarmine and Alcian blue stains revealed only the presence of intraductal mucinous material. An immunohistochemical panel (Table 2) was performed to further characterize the neoplastic cells. The tumor cells were diffuse and strongly positive for pan-cytokeratin (CK) AE1/AE3, 34betaE12 CK, vimentin, p63 and S100 (Fig. 2a–e). Moreover, CK7 and EMA strongly stained the ductal structures (Fig. 2f–g), while those solid areas also showed diffuse and moderate expression of CD56 (Fig. 2h). Podoplanin (D2-40), Calponin (Fig. 2i–j) and GFAP (not shown), followed by DOG-1 (mainly membranous staining pattern), were focally positive (Fig. 2k), whereas α -SMA and h-Caldesmon (included due to the suggestive myoepithelial profile), as well as CK20, CD57, ERBB2/HER2 (not shown) and p53 (not shown) were negative (Fig. 2l–o). Ki-67 was <2% (Fig. 2p). Interestingly, the morphological evaluation revealed scarce clear cells within solid areas, some of them containing pigment granules, suggesting represent macrophages; however, CD11c, CD68 and CD163 were negative. Notably, consecutive serial tissue sections using CD57

Table 1 Clinicopathological features of previously published cases of melanin-pigmented salivary gland tumors

Author, year	Cases	Diagnosis	Site	Melanin location	Gender	Mean age	Ethnicity
Buchner and David, 1977 [8]	18*	Wartin's tumor	Parotid gland	Intracytoplasmic; stromal cells	Not described	56	Not described
Aufdemorte et al., 1985 [9]	1	Mucoepidermoid carcinoma	Buccal mucosa	Intracytoplasmic; stromal cells	Female	32	Caucasian
Takeda, 1996 [14]	1	Adenoid cystic carcinoma	Hard palate	Intracytoplasmic; stromal cells	Female	63	Japanese
Takeda et al., 2004 [15]	1	Pleomorphic adenoma	Soft palate	Intracytoplasmic; stromal and tumor cells	Male	33	Japanese
Marucci et al., 2005 [10]	1	Mucoepidermoid carcinoma	Retromolar trigone	Intracytoplasmic; stromal and tumor cells	Female	36	Not described
Sekine et al., 2005 [11]	1	Mucoepidermoid carcinoma	Hard palate	Intracytoplasmic; stromal and tumor cells	Female	26	Japanese
Desai and Borges, 2006 [16]	1	Adenoid cystic carcinoma	Nasal cavity	Intracytoplasmic; stromal and tumor cells	Male	42	Not described
Takeda & Kurose, 2006 [12]	1	Mucoepidermoid carcinoma	Lower lip	Intracytoplasmic; stromal and tumor cells	Male	42	Japanese
Liyanage et al., 2014 [13]	1	Mucoepidermoid carcinoma	Floor of the mouth	Intracytoplasmic; stromal cells	Female	34	Not described
Current case, 2017	1	AdCaNOS	Buccal fornix	Intracytoplasmic; tumor cells	Female	45	African–American

In almost all cases, stromal cells were considered represent melanocytes

*A total of 21 cases (19 males and 2 females) of Warthin's tumor were analyzed. Of them, only 18 cases presented pigmentation

confirmed the perineural invasion (CD56 and CD57 were included for assessing tumor cells invading neural bundles, being helpful only CD57) (Fig. 2o). By histochemistry, the pigment granules (Fig. 3a) were negative for PAS, with and without diastase (Fig. 3b) and positive for Fontana-Masson stain (and potassium permanganate bleaching-sensitive) (Fig. 3c, d). Ziehl-Neelsen, Perls and colloidal iron stains were negative. In addition, foci of pigment granules were highlighted with HMB-45 (Fig. 3e) and MART-1/Melan-A (Fig. 3f) antibodies, suggesting the presence of melanosomes. The correlation of the microscopic, histochemical and immunohistochemical findings was consistent with the diagnosis of low-grade AdCaNOS with intracytoplasmic melanin granules. No recurrences were observed within a 2-year follow-up period.

Discussion

The presence of pigments in salivary gland neoplasms is poorly discussed. Several melanin-containing salivary gland tumors have been reported (Table 1). Melanin has several metabolic pathways and can be classified into eumelanin, pheomelanin, neuromelanin and pyomelanin [18]. There are

reports of melanin pigmentation in Wartin's tumor [8], MEC [9–13], AdCC [14, 15] and PA [16], all of which were associated with the presence of stromal melanocyte-like cells, while some cases also presented intratumoral cytoplasmic melanin pigment [10–12, 15, 16]. Lipofuscin is a pigment that can be found in the brain, heart and liver. It is believed that this pigment has increased deposition over time [19]. The exact role or deposition pattern of this pigment is not fully elucidated; however, the presence of lipofuscin granules may give evidence of the age of the patients. Interestingly, lipofuscin pigmentation has been described affecting salivary gland tumors. Buchner & David [19] suggested that lipofuscin granules involving benign tumors can be found in both epithelial and stromal cells, whereas malignant neoplasms preferably will have deposits of lipofuscin in the tumor stroma. In fact, it has been shown that plasmacytoid cells were the cellular type preferentially carrying the lipofuscin granules in a PA case [17]. However, sometimes the differentiation between melanin and lipofuscin can be challenging. Both melanin and lipofuscin are positive for Fontana-Masson stain; however, only melanin can be removed from organic materials with bleaching techniques using potassium permanganate and oxalic acid or hydrogen peroxide [20]. Lipofuscin, but not melanin, is positive for

Fig. 1 Microscopic view; H&E staining. **a** Solid tumor mass, with high cellularity, showing a lobular configuration; $\times 10$. **b** Neoplastic cells admixed with ductal structures, supported by hyaline stroma; $\times 10$. **c** Glandular/ductal structures permeated by clear cells; $\times 40$. **d** Minute ductal structures (arrows) and sebaceous-like cells (asterisk); $\times 40$. **e** Tumor cells showing evident perineural invasion (arrow); $\times 40$. **f** Notice the residual salivary gland duct (arrow) surrounded by tumor cells, $\times 20$

PAS stain, and variably positive for Ziehl-Neelsen stain. In the present case, the pigment granules were positive for Fontana-Masson stain (and potassium permanganate bleaching-sensitive) and negative for PAS and Ziehl-Neelsen stains. In addition, foci of pigment granules were highlighted with HMB-45 and MART-1/Melan-A antibodies, suggesting the presence of melanosomes. Thus, the pigment was classified as melanin, mainly in intratumoral cytoplasmic location. Moreover, pigment-containing cells presenting a dendritic morphology were not observed, ruling out the possibility of the presence of melanocyte-like cells. Recently, a low-grade MEC with marked differentiation toward non-epithelial spindle cells expressing melanocytic markers [21], as well as a low-grade MEC with both melanin pigmentation and spindle cell differentiation have been reported [13], which support the findings of the current case (especially regarding the S100, HMB-45 and MART-1/Melan-A positivity).

Melanocytes are originated from the neural crest and can be found in human oral mucosa of healthy patients [22]. Since minor salivary glands arise as epithelial buds in the oral cavity, it is expected to be present in normal and neoplastic salivary glands. However, since myoepithelial cells also originate in the neural crest, these cells could have the ability to produce melanin, similar to melanocytes, considering their common embryological origin [16, 22]. This could explain the findings of the present case, especially due to its myoepithelial differentiation profile [22].

In the United States, salivary gland malignant tumors represent 0.3% of all malignancies and 6% of all head and neck cancers [23]. Overall, tumors arising from minor salivary glands represent 9–23% of all salivary gland tumors, and of them, malignant tumors account for 40–54% [24]. Salivary AdCaNOS is a malignant neoplasm with ductal or glandular differentiation [2]. Microscopically, AdCaNOS is

Table 2 Histochemical and immunohistochemical analyses of the intraoral pigmented low-grade AdCaNOS

	Ductal/ glandular structures	Solid areas	Tumor stroma	Pigment	Details
Histochemical analysis					
Periodic acid Schiff stain with diastase digestion	–	–	–	–	Foci of intraluminal mucinous material positive
Periodic-acid Schiff stain without diastase digestion	–	–	–	–	Foci of intraluminal mucinous material positive
Mucicarmine stain	–	–	–	–	Foci of intraluminal mucinous material positive
Colloidal iron staining	–	–	+ focal	–	Foci of intraluminal mucinous material positive
Perls stain	–	–	–	–	Foci of hemosiderin granules positive
Fontana Masson stain	–	–	–	1+	Potassium permanganate bleaching-sensitive
Alcian blue stain	–	–	+ focal	–	Foci of intraluminal mucinous material positive
Ziehl-Neelsen stain	–	–	–	–	
Immunohistochemical analysis					
<i>Antibody (Clone; dilution; manufacturer)</i>					
pan-CK (Clones AE1/AE3; 1:500; Dako [#])	3+	3+			
CK7 (Clone OV-TL 12/30; 1:500; Dako [#])	3+	1+			
CK20 (Clone Ks20.8; 1:500; Dako [#])	–	–			
Vimentin (Clone Vim 3B4; 1:500; Dako [#])	–	3+			
α-SMA (Clone 1A4; 1:500; Dako [#])	–	–			Scarce positive cells in close relationship with residual salivary gland ducts
Calponin (CALP; 1:300; Abcam ⁺)	–	1+			
h-Caldesmon (E-89; 1:40; Cell Marque [†])	–	–			
DOG-1 (K9; 1:100; Leica*)	–	1+			
34βE12 CK (34Be12; 1:300; Dako [#])	3+	2+			
S-100 (Polyclonal; 1:3000; Leica*)	3+	3+			
GFAP (Clone 6F2; 1:500; Dako [#])	–	1+			
Podoplanin (Clone D2-40; 1:500; Dako [#])	–	1+			
EMA (Clone E29; 1:500; Dako [#])	2+	–			Scarce positive cells in solid areas
p63 (Clone DAK-p63; 1:500; Dako [#])	–	3+			
CD68 (Clone KP1; 1:3000; Dako [#])	–	–			
CD163 (Clone 10D6; 1:500; Leica*)	–	–			
CD11c (Clone 5D11; 1:500; Leica*)	–	–			
CD56 (Clone CD564; 1:100; Leica*)	1+	3+			
CD57 (Clone TB01; 1:600; Dako [#])	–	–			
ERBB2/HER2 (SP3; 1:200; Cell Marque [†])	–	–			
HMB45 (Clone HMB45; 1:500; Dako [#])	1+	1+			
MART-1/Melan-A (A103-MART-1; 1:120; Cell Marque [†])	1+	1+			
p53 (Clone DO-7; 1:500; Leica*)	–				
Ki-67 (Clone SP6; 1:500; Abcam ⁺)	<2%				

Negative: –; Positive 1+: 5–25% of the tumor cells positive; Positive 2+: > 25–75%; Positive 3+: > 75%

Antigen retrieval was performed using 10 mmol/l citrate buffer (pH 6.0)

*Leica Biosystems Newcastle Ltd; Newcastle, United Kingdom

[#]Dako; Agilent Technologies, Inc., Glostrup, Denmark

⁺Abcam; Cambridge, United Kingdom

[†]Cell Marque; Sigma Aldrich Company, Darmstadt, Germany

Fig. 2 Immunohistochemical findings. **a** Strong positivity for pan-CK AE1/AE3; $\times 20$. **b** 34betaE12 CK expression was uniform, highlighted ductal structures; $\times 10$. **c** Vimentin was uniformly positive in tumor cells; $\times 20$. **d** Numerous tumor cells showed nuclear positivity for p63; $\times 40$. **e** Uniform and strong positivity for S100 in tumor cells; $\times 20$. **f** CK7 highlighted mainly ductal structures; $\times 20$. **g** EMA highlighted the luminal surfaces; $\times 40$. **h** Large areas showing CD56 positivity in tumor cells; $\times 40$. **i** Foci of mainly non-luminal cells were D2-40 positive; $\times 40$. **j** Calponin showed focal expression; $\times 20$.

k Focal membranous expression of DOG-1 in tumor cells; $\times 20$. **l** α -SMA was negative in tumor cells. Notice myoepithelial cells (black arrows) surrounding a residual ductal structure, being permeated by tumor cells; $\times 20$. **m** h-Caldesmon was uniformly negative; $\times 20$. **n** CK20 was uniformly negative; $\times 20$. **o** Tumor cells were CD57 negative; $\times 40$. Notably, due to the uniform positivity of S100 and CD56, only CD57 evidenced perineural invasion (arrow). **p** Ki-67 labeling index was $< 2\%$; $\times 40$.

characterized by wide spectrum of architectural patterns, which may include glandular structures, papillary, cystic, cribriform or solid pattern. AdCaNOS should be considered in the differential diagnosis of tumors with considerable heterogeneity of growth patterns that cannot clearly be classified as other well-established adenocarcinoma entities [2, 25].

Data on relative frequency of AdCaNOS range from 1.2 to 19.0% of all salivary gland malignant tumors, and of them, about 40% originate from minor salivary glands [2, 6, 26]. Although there is divergence in the literature, it is believed that the average age of involvement is around 58 years [1] with male predilection (4:1 ratio) [2] and 15-year survival rates for low-, intermediate- and high-grade tumors accounting for 54, 31 and 3%, respectively [1, 27]. The site of greatest involvement differs among several studies; however, the

main sites affected include the parotid glands, minor salivary glands (especially the palate) and submandibular salivary glands [5]. In most cases, the lesion appears as a fibrous, solid and painless mass that may be ulcerated and infiltrating adjacent tissues. In intraoral tumors, chronic irritation, such as rubbing of the removable prosthesis, can cause secondary pain sensibility [2, 26, 28, 29].

Low-grade malignant salivary gland tumors, including AdCaNOS, comprise a distinctive group which can mimic benign salivary gland tumors, since there are no evident pleomorphic cells, mitotic activity or necrosis areas, leading to misdiagnosis; however, perineural invasion and foci of infiltration of the residual salivary gland parenchyma can be noticed, which are not seen in benign tumors [1, 28, 30].

The differential diagnosis of salivary low-grade AdCaNOS include PA, basal cell adenoma (BCA),

Fig. 3 Histochemical findings. **a** H&E staining showing intracytoplasmic pigment granules in non-luminal cells. **b** The pigment granules were negative for PAS stain, with and without prior diastase digestion. **c** Fontana-Masson stain revealed uniform strong positivity. **d** Pigment granules were bleaching-sensitive with potassium permanganate, as shown by negativity for Fontana-Masson stain. **e** HMB45 and **f** MART-1/Melan-A antibodies highlighted foci of pigment granules (black arrows), suggesting presence of melanosomes within tumor cells. Notice the residual melanin pigment (star) (all cases, $\times 40$)

epithelial-myoepithelial carcinoma (EMC), polymorphous adenocarcinoma (PAC), clear cell carcinoma (CCC), myoepithelial carcinoma, acinic cell carcinoma (AcCC), intraductal carcinoma (so-called low-grade cribriform cystadenocarcinoma), low-grade MEC, AdCC (without solid component) and basal cell adenocarcinoma. Moreover, carcinoma ex-PA with low-grade histology (especially myoepithelial carcinoma) should also be considered [1, 31].

In the current case, the typical arrangement of luminal and abluminal cells present in PA was not observed. Moreover, perineural invasion and foci of infiltration of residual glandular parenchyma are not in agreement with a benign course of PA. BCA is a rare benign salivary gland neoplasm. There are four types of BCA defined as solid, tubular, trabecular and membranous. This neoplasm presents moderate to high cellularity, with cells arranged in tubules or trabeculae, sometimes forming clusters, cords, sheets or islands. Peripheral cells show palisade-like arrangements, and the

cells at the center of the basaloid nests are generally less stained and without polarization [32]. In the current case, these microscopic features were not observed, whereas perineural invasion was evident. Moreover, the CK7 positivity was irregular, and α -SMA staining was practically absent, different from BCA.

EMC is a malignant neoplasm, usually of low-grade, often showing a multinodular growth pattern. This neoplasm is classically composed of two populations: epithelial and myoepithelial cells. The former population defines a ductal architecture, while the latter population is localized peripherally and presents classically clear cytoplasm [33, 34]. Different from current case, in EMC the typical bilayered arrangement of inner ductal cells and outer myoepithelial cells is highlighted by immunohistochemistry. PAC is the second more common intraoral malignant salivary gland tumor composed by cells with cytological uniformity, an architectural heterogeneity and

an infiltrative growth pattern [18, 35]. The tumor cells are small to medium-sized with oval nuclei and occasional nucleoli. The main architectural patterns of the PAC such as trabecular, microcystic, cribriform, papillary-cystic and indian-file pattern were not observed in the current case. Moreover, we noticed mild pleomorphism, clear cells and glandular/ductal structures, which are uncommon in low-grade PAC cases [34].

CCC frequently occurs in the oral cavity, especially in the palate and base of the tongue. This is a low-grade malignant salivary gland neoplasm, microscopically presenting large areas of clear cells with distinctive cell borders, supported by hyalinized eosinophilic material. These tumor cells are arranged in sheets, cords, nests and trabecular patterns. Perineural and/or vascular invasion may be visualized [1]. PAS and mucicarmine stains reveal the presence of cytoplasmic glycogen and mucin (this latter scarce and punctate). In the current case, numerous clear cells and foci of hyalinized stroma were also observed, strongly raising the possibility of CCC. However, glandular/ductal structures were frequent, as well as morphological cellular diversity including sebaceous-like, oncocytoid and columnar cell types. Moreover, clear cells were negative for PAS and mucicarmine stains, and by immunohistochemistry, different from CCC, the current case was positive for vimentin, S100, and focally for GFAP, podoplanin (D2-40), Calponin and DOG-1, supporting a myoepithelial-like differentiation. While uniform and strong expression of DOG-1 is typical of AcCC, it has been shown that a subset of biphasic salivary gland malignant tumors can exhibit a DOG-1 positive ‘transformed’ myoepithelial phenotype [36], such as observed in the current case. Although myoepithelial carcinoma (especially, clear cell variant) could be considered by these immunohistochemical findings, the presence of glandular/ductal structures, the lack of typical plasmacytoid, epithelioid and spindle cellular types, as well as the α -SMA negativity, argue against this possibility [1].

In summary, salivary low-grade AdCaNOS is a malignant neoplasm with apparently favorable course and good prognosis. Because of its histomorphological features, often mimicking benign or low-grade malignant epithelial neoplasms, this tumor can be misdiagnosed, added to the fact that low-grade AdCaNOS cases are poorly reported in the English literature. Here, we reported an unusual case with detailed histochemical and immunohistochemical analyses, emphasizing that AdCaNOS presents microscopic features different from other malignant salivary gland tumors. The presence of melanin in these tumors seems to have no impact on the prognosis.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study formal consent is not required.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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