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Evaluation of facial artery course variations and depth by Doppler ultrasonography

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Abstract

Background: As deep nasolabial folds (NLF) are associated with facial aging, there is an increasing demand for esthetic correction with filler injections. Understanding the anatomy of the angular artery (AA) and facial artery (FA) around the NLF region is essential for ensuring the safety of dermal filler injections into the NLF. The purpose of this study was to provide detailed vascular anatomical information on the course and depth of AA and FA around NLF using Doppler ultrasound on live cases.

Methods: FA was observed from the origin level adjacent to the mandible corpus to the end of its terminal branch AA in 168 hemifaces of 84 cases with Doppler ultrasonography.

Results: We made a classification of the FA course based on the NLF. The minimum and maximum depths of the FA along its course were measured in 84 cases. The results showed that its course may be highly superficial (2.5 mm at the mandibular origin, 3.7 mm at the cheilion, 3.7 mm at the nasal ala) or it may follow a very deep course near the periosteum (15.0 mm at the mandibular origin, 18.7 mm at the cheilion, 23.5 mm at the nasal ala). FA depth was varied between 5.98 mm and 6.62 mm at the mandibular origin, between 8.36 mm and 9.20 mm at the cheilion, between 9.52 mm and 10.51 mm at the nasal ala at a 95% confidence interval.

Conclusions: This study suggests that there is no absolutely safe depth or region for nasolabial fold filler injections.

KEYWORDS

angular artery, arterial depth, dermal filler, Doppler ultrasonography, facial artery, nasolabial fold

1 | INTRODUCTION

Prominent nasolabial folds (NLFs) are one of the most noticeable signs of facial aging which negatively affect self-confidence often leading to a person's desire to improve their appearance using dermal fillers. Injecting fillers to correct skin folds and wrinkles have dramatically increased in popularity and become a standard therapeutic method in modern cosmetic practice, and 2.6 million soft tissue filler procedures were conducted in the United States in 2018.[1]

As the popularity of soft tissue fillers increases, so do the adverse events. The most feared complication following the use of injectable fillers is intraarterial injection, which has a relatively low incidence but its consequences cutaneous necrosis and blindness are devastating. The incidence of vascular occlusion has been estimated at 3 per 1000 for calcium hydroxyapatite, and 3-9 per 10 000 for hyaluronic acid products, but the true incidence of this complication is unknown because of underreporting by clinicians. Studies showed that, NLF and nose are the most common points at which intravascular injections occurred, followed by the forehead and glabella, and

then the lower lip, accordingly most risk-associated blood supply is the central column of the face including the facial artery (FA) (branch of external carotid artery) and its branches in the central part of the face.[2]

The internal carotid system supplies the upper external nose through the dorsal nasal artery (DNA), which originates from the ophthalmic artery (OA).[3] The mechanism of blindness after filler injection has been hypothesized to involve intraarterial injection of filler to the FA branches followed by subsequent retrograde embolization into the OA system through the anastomoses between these two systems. These anastomoses make nose, NLF and glabella locations most dangerous locations for ocular complications.[2,4,5] Catastrophic cutaneous necrosis after an intraarterial filler injection can be avoided in most cases with good management, in which the affected area usually heals with minimal scarring. However, no treatments have been found to be consistently successful in treating blindness, and most cases of vision loss did not recover.[2,4,5] In a recent review, 48 new published cases of partial or complete vision loss after filler injection were identified between 2015 and 2018. The sites that were highest risk were the nasal region (56.3%), glabella (27.1%), forehead (18.8%), and NLF (14.6%).[5] NLF runs a parallel course with the underlying angular artery (AA), which makes it one of the most dangerous areas for intraarterial filler injection. To reduce the possibility this complication, it is critical for injecting physicians to have a thorough knowledge of the vascular anatomy and to understand key prevention strategies for safe injection techniques.

Although different definitions have been made for the AA,[6,7] AA is defined as the terminal branch of FA anatomically.[8] Cadaver studies have been conducted involving morphometric measurements to chart the course of FA and AA [9-11]; a further cadaver study used computed tomography (CT) to map the arterial structures of the entire facial region [12]; and a Doppler ultrasonography study investigated only nasal vascularity.[13] No study has been identified in English literature to investigate both AA and FA in live cases using Doppler ultrasonography.

Color Doppler ultrasound is a noninvasive imaging method that has proven to be helpful, when used in common dermatological conditions such as vascular abnormalities, benign and malignant cutaneous tumors, and some inflammatory diseases.[14] The clinician can also use the ultrasonographic modality with color Doppler used in this study in real time to avoid vascular complications during treatment. However, the possibility of false negativity was also discovered.[15,16] The present study charts the course and depth of the AA, thereby demonstrating the detailed vascular anatomy of the AA and the FA in live cases, which is required to ensure safe clinical manipulations when injecting fillers to NLFs.

2 | MATERIALS AND METHODS

This study was conducted in the Radiology Department between February 2016 and October 2016. The patients were referred to our department from Dermatology Department for superficial duplex Doppler sonographic measurements of the face for various clinical indications. All patients included in this study provided their informed consent. The approval of the Ethics Board for nonpharmacologic clinical trials was obtained to conduct this study (No. 206/2019). The study is performed in a Caucasian Turkish population. The patients who had a history of facial trauma or surgery and had congenital facial deformity or an inflammatory facial condition were not included in the study. Superficial duplex Doppler ultrasonography was performed in 168 hemifaces of 84 cases. All sonographic examinations were performed by one radiologist experienced in ultrasonography for 12 years. An ultrasound device (Aplio 500; Toshiba Medical System Corporation, Tokyo, Japan) with a multifrequency linear-array transducer (14Hz) was used. Examinations were performed with B mode and color Doppler ultrasonography images. Both facial halves of all cases were examined separately. The patients were evaluated in supine position with head and shoulders elevated, similar to the filler injection position.

FA was observed from the origin level adjacent to the mandible corpus to the end of its terminal branch AA. Based on the detailed course and origin of the structures around AA, 4 patterns were detected separately in both hemifaces (Figure 1). In Type A (permanent pattern), AA passes from the branching point of the lateral nasal artery (LNA) to the medial canthal area. In this pattern, AA is located adjacent to the lateral edge of the nose and joins the branch of the OA at the lateral side of radix of the nose. In Type B (variant pattern), AA originates from FA near the mouth corner (cheilion) and then advances toward the infraorbital area, eventually medial to the nasojugal and medial canthal area. In Type C (alternative pattern), AA originates from OA and extends downward along the lateral side of the nose. In type D (latent pattern), FA ends as LNA without forming an AA branch.

The course variation of FA with respect to the NLF was found to be 4 patterns in both hemifaces (Figure 2). In type I, FA is parallel and inferior to the NLF. In type II, FA is parallel and superior to the NLF. In type III, FA crosses the NLF from inferior to superior. In type IV, FA crosses the NLF from lateral to medial.

The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Body mass index comparative FA depth measurements were performed at the level of mandibular origin of FA (Figure 3A), at the level of cheilion (Figure 3B), and at the level of the nasal ala inferior (Figure 3C). The distance from the upper wall of the FA to the skin was measured in millimeters. Skin-mandibular distance was measured at the level of mandibular origin of FA, and skin-maxilla distance was measured at the level of nasal ala inferior. FA diameter at the mandibular origin level of FA was also included in the measurements (Figure 3D).

2.1 | Statistical analysis

Numbers and percentages were given as descriptive statistics for categorical parameters. The distributions of the variables across the study groups were tested with the Shapiro-Wilks test. The parameters

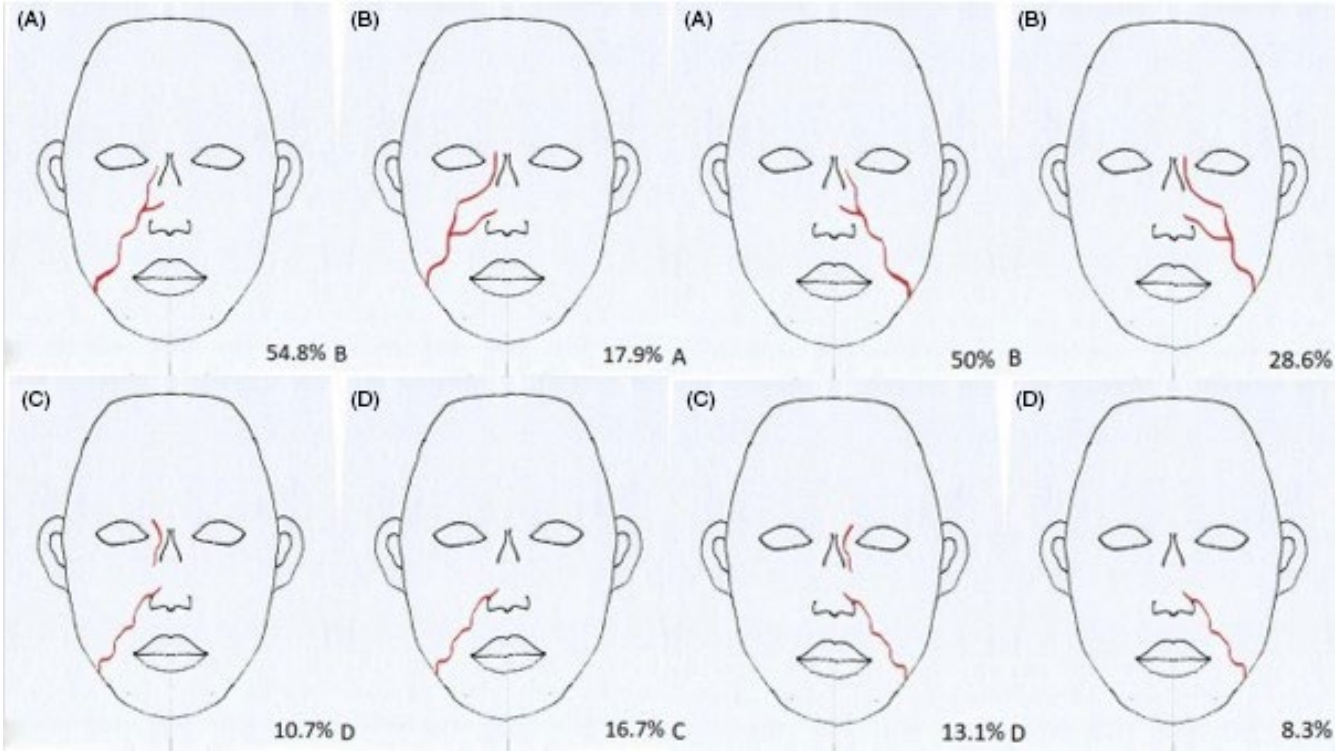

FIGURE 1 AA course variation in right and left hemifaces. Schematic diagrams show 4 course variations of AA. A) Type A, B) Type B, C) Type C, D) Type D. 1. Type A (permanent pattern): AA originates from the branching point of the lateral nasal artery (LNA) adjacent to the nose wing and extends to the forehead. 2. Type B (variant pattern): AA is the continuation of the variant branch of FA, advancing vertically to the nasojugal and medial canthal regions. 3. Type C (alternative pattern): AA originates from the ophthalmic artery (OA) in the medial canthal region. 4. Type D (latent pattern): AA is not developed

were found to be normal distribution. Continuous data were expressed as mean ± standard deviation. In addition, depth averages and 95% confidence intervals for the averages were calculated. In the analysis of categorical data, the Fisher exact chi-square test was used. Two-tailed $P < .05$ was considered statistically significant. Variance analysis was used to check whether there was a difference between the mean depth of FA course and AA variations. Tukey test was used to compare the groups in pairs. Pearson correlation coefficient was used to calculate linear relationships between BMI and depths.

3 | RESULTS

The percentage of male and female patients were 47.6% and 52.4%, respectively. The minimum age for both males and females were 19, the maximum age for males and females were 67 and 77 years old, respectively. The mean age for males and females were 38.1 ± 13.7 and 45.9 ± 8.5 years old, respectively.

The course variation of AA evaluated. Type A was observed in 46 cases (54.8%) in the right hemiface and 42 cases (50%) in the left hemiface. Type B is observed in 15 cases (17.9%) in the right hemiface and in 24 cases (28.6%) in the left hemiface. Type C is observed in 9 cases (10.7%) in the right hemiface and in 11 cases (13.1%) in the left hemiface. Type D was observed in 14 cases (16.7%) in the right hemiface and in 7 cases (8.3%) in the left hemiface. When AA variations in right hemiface and left hemiface were compared, no statistically significant relationship was observed between the distribution of variations (Table 1). In 33 (39.3%) of 84 cases, AA course variations were symmetrical. Type A in 28 cases, type B in 8 cases, type C in 2 cases, and type D in 1 case were observed in both hemifaces. There was no statistically significant relationship between the distribution of variation of AA in the right and the left hemifaces ($P = .260$).

The course variation of FA according to NLF can be classified into 4 groups. Type I is seen in 30 cases (35.7%) in the right hemiface and 31 cases (36.9%) in the left hemiface. Type II is seen in 15 cases (17.9%) in the right hemiface and 16 cases (19.1%) in the left hemiface. Type III is seen in 21 cases (25%) in the right hemiface and 27 cases (32.1%) in the left hemiface. Type IV is seen in 18 cases (21.4%) in the right hemiface and 10 cases (11.9%) in the left hemiface. When FA course variations were compared to the NLF in the right and left hemifaces, there was a statistically significant relationship between the distribution of variations (Table 2). In 51 (60.7%) of 84 cases, FA course variations were symmetrical. Type I in 19 cases, type II in 11 cases, type III in 12 cases, and type IV in 9 case were observed in both hemifaces. There was a statistically significant relationship between the distribution of FA course variation in the right and the left hemiface ($P < .001$).

FA depth measurements were performed at the level of mandibular origin of FA, cheilion level and nasal ala inferior level (base

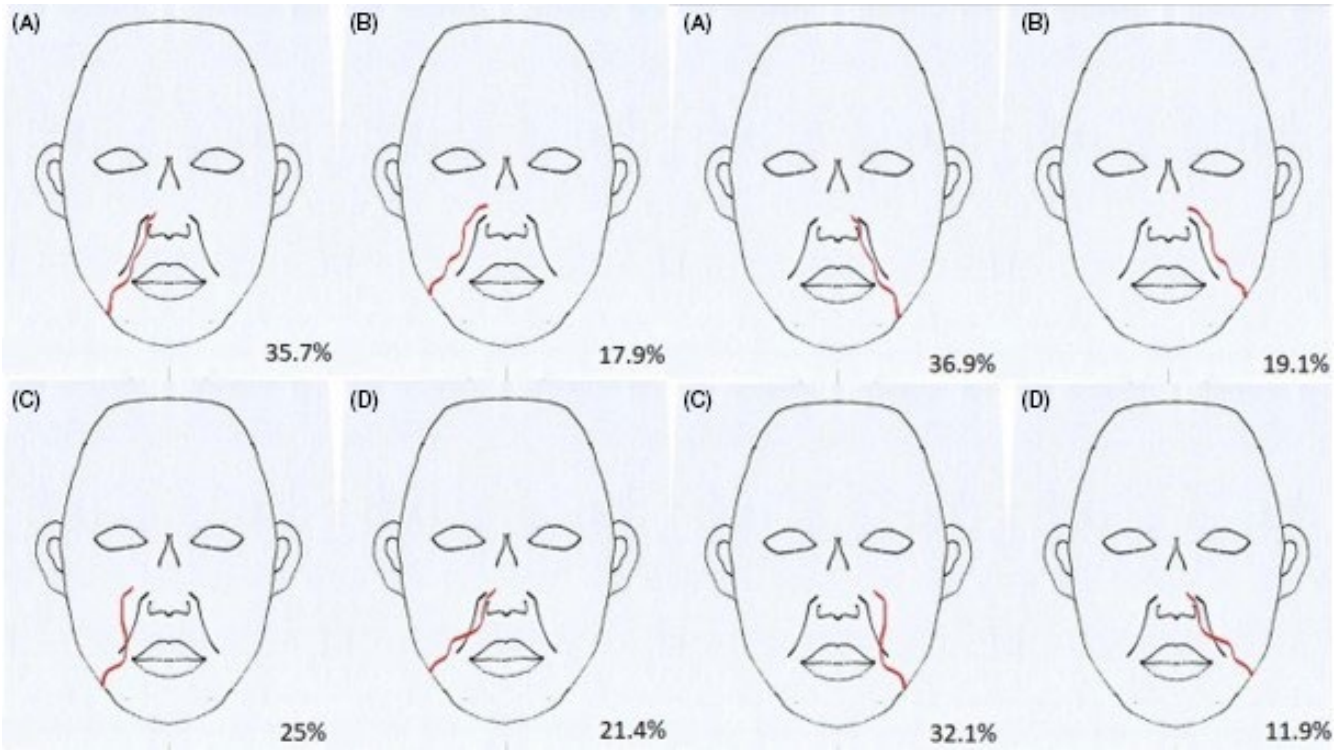

FIGURE 2 FA course variation according to NLF in right and left hemifaces. Schematic diagrams show 4 course variations of FA relative to NLF. A) Type 1, B) Type 2, C) Type 3, D) Type 4. 1. Type I: FA is parallel and inferior to the NLF. 2. Type II: FA is parallel and superior to the NLF. 3. Type III: FA crosses the NLF from inferior to superior. 4. Type IV: FA crosses the NLF from lateral to medial

of the nasal ala). The depth at which FA passes through the minimum-maximum depth, mean depth, and 95% confidence interval without distinction between the right-left hemiface was identified (Table 3).

At the origin level of the mandible of FA, FA diameter was minimum 0.8 mm, maximum 2.2 mm, mean 1.56 ± 0.35 mm. BMI was measured as minimum 16.78 (kg/m^2) and maximum 62.49 (kg/m^2) in patients with a mean of 28.31 ± 7.48 (kg/m^2). There was a statistically high-intermediate linear relationship between BMI and skin-FA depth and skin-bone (mandible and maxilla) depths (Table 4).

The relationships between AA variation and skin-FA and skin-bone (mandible and maxilla) depths were evaluated in both hemifaces. The difference between A and B variations in the skin - average FA depth at the cheilion level in the right hemiface was statistically significant (P = .014). There was no statistically significant difference between AA variations in all other measurements made on both hemifaces regarding depth averages (Tables 5,6). On the right hemiface, the variation B in the skin - average FA depth at the level of cheilion is deeper than the variation A.

The relationship between FA course variation and skin-FA, skin-bone (mandible and maxilla) depths were evaluated in both hemifaces. The difference between the skin - bone average depth at FA mandibular origin in both hemifaces was not statistically significant (P = .058 on the right, P = .130 on the left). The difference between the averages of depths was statistically significant in all other measurements in both hemifaces (Tables 7,8).

The 2nd variation was located deeper than the 1st variation at all levels in the right hemifaces. This was the main difference in the right hemifaces. The other distinction was that the 4th variation was deeper than the 1st variation at inferior nasal ala (Table 9).

When the differences in the left hemifaces were examined, the main difference was that the FA was located deeper than the other variations in the 2nd variation at the level of cheilion and inferior nasal ala. The other distinction was that the 2nd variation at the mandibular origin level of FA in the left hemiface was located deeper than the 1st variation (Table 9).

According to the course of FA, FA (Type II) course at the superior of the NLF is relatively deeper than the other variations in both hemifaces.

There is a statistically significant relationship between the variation of the AA and the FA course variation in the right hemiface (P: .002) (Table 10).

There is a statistically significant relationship between the variation of the AA in the left hemiface and the FA course variation (P: .01) (Table 11).

4 | DISCUSSION

Injectors should be familiar with the anatomy (location and depth) of facial vessels and the common variations at different injections sites. The NLF is one of the most common injection sites during cosmetic

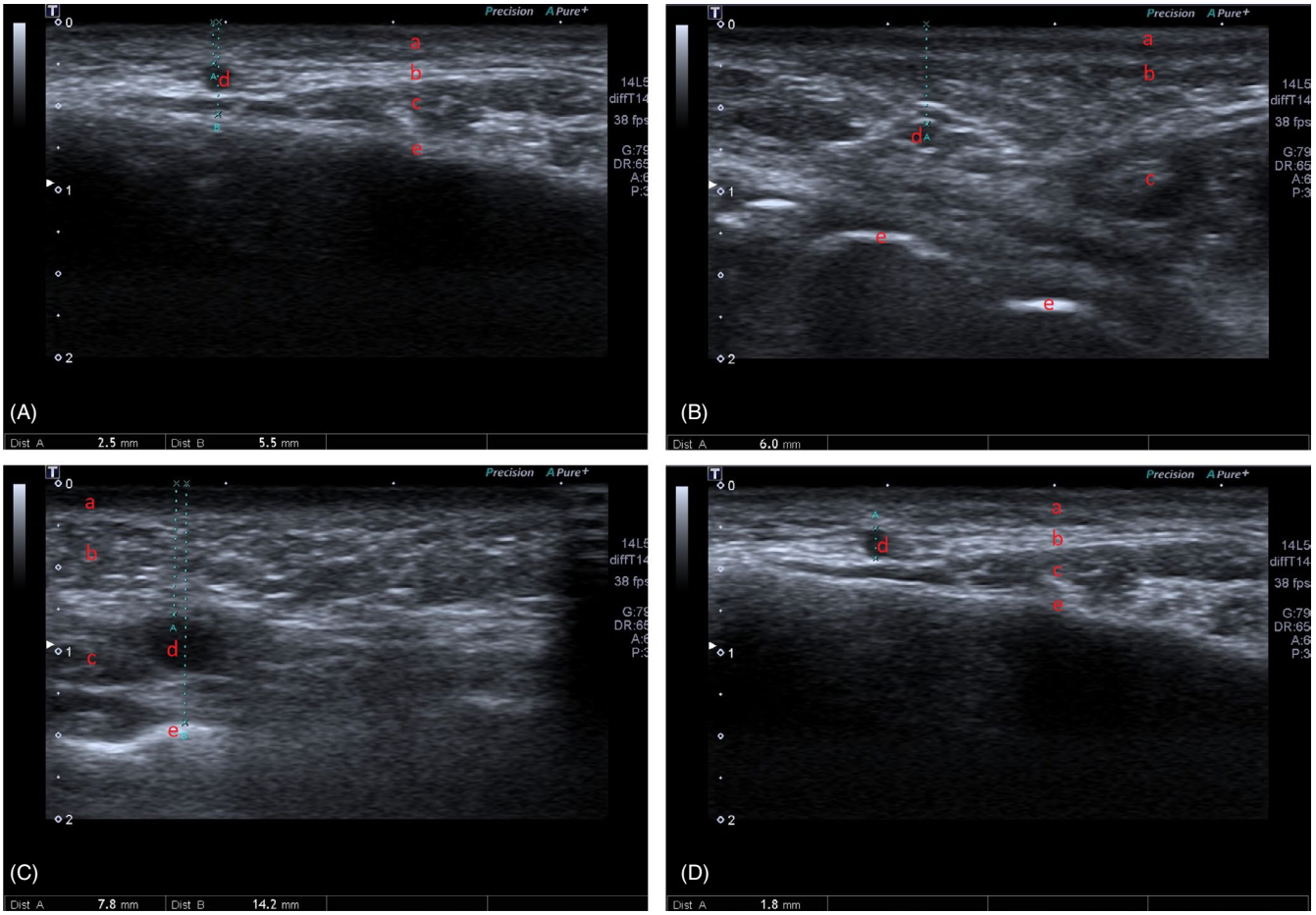

FIGURE 3 Skin-facial artery and skin-bone depth measurements from the level of mandibular origin of FA [a-dermis and subcutaneous tissue, b-fascia masseterica, c-masseter muscle, d-artery, e-mandibular bone] (A), from the level of cheilion [a-dermis, b-subcutaneous tissue, c-orbicularis oris muscle, d-artery, e-teeth] (B), and from the level of nasal ala inferior [a-dermis, b-subcutaneous tissue, c-levator labii superioris muscle, d-artery, e-maxillary bone] (C). FA diameter at the mandibular origin level of FA [a-dermis and subcutaneous tissue, b-fascia masseterica, c-masseter muscle, d-artery, e-mandibular bone] (D)

TABLE 1 Comparison of AA course variation in right and left hemifaces

		Left AA variation (A,B,C,D)				
		A	B	C	D	
		n (%)	n (%)	n (%)	n (%)	*P*
Right AA variation (A,B,C,D)	A	28 (66.7)	10 (41.7)	5 (45.5)	3 (42.9)	.260
	B	4 (9.5)	8 (33.3)	1 (9.1)	2 (28.6)	
	C	5 (11.9)	1 (4.2)	2 (18.2)	1 (14.3)	
	D	5 (11.9)	5 (20.8)	3 (27.3)	1 (14.3)	

Abbreviation: n, number.

procedures, being the area where the AA originates from the FA. This area has been linked to such serious complications as skin necrosis and blindness due to retinal artery occlusion.[2] Such side effects can be avoided by obtaining detailed and accurate information about the anatomical location of the AA prior to the initiation of filler injection procedures to the NLFs. Investigating the treatment site before and after the filler injection treatment can dramatically reduce complications and adverse outcomes.[17]

Although it is widely known that AA predominantly extends across the NLF on the lateral side of the nose, most previous studies have focused only on the clinical definitions of the course of the AA given in anatomy textbooks.[18] Niranjan et al reported that AA was ended as a terminal branch of the FA in 68% of the specimens.[7] Nakajima et al reported this ratio as 72%.[19] The present study focus on the Turkish population; the AA is observed in 83.3% of people on the right hemiface and in 91.7% on the left hemiface. A study by

TABLE 2 Comparison of FA course variation according to NLF in right and left hemifaces

		Left FA course variation (1,2,3,4)				
		1	2	3	4	
		n (%)	n (%)	n (%)	n (%)	*P*
Right FA course variation (1,2,3,4)	1	19 (61.3)	2 (12.5)	8 (29.6)	1 (10)	<0.001
	2	0 (0.0)	11 (68.8)	4 (14.8)	0 (0.0)	
	3	8 (25.8)	1 (6.3)	12 (44.4)	0 (0.0)	
	4	4 (12.9)	2 (12.5)	3 (11.1)	9 (90)	

P < 0.001: statistical significance value.

TABLE 3 Depth measurements of FA in all three planes with minimum, maximum, average, and 95% confidence interval

	Min-Max (mm)	Mean-[CI] (mm)
FA depth at the origin of the mandible of FA	2.5- 15.0	6.30-[5.98-6.62]
FA depth at cheilion	3.7- 18.7	8.78-[8.36-9.20]
FA depth at inferior nasal ala	3.7- 23.5	10.02-[9.52-10.51]

Abbreviations: CI, clearance; Max, maximum; Min, minimum; mm; millimeter.

Wu et al involving 12 cadavers identified the AA in 13 facial halves of only seven samples. In samples without an AA, there is no direct anastomosis between the FA and OA.[20] It is observed that in type D (latent pattern), blood is not supplied from the OA to the lateral side of the nose and tear duct in the absence of an AA. Given that the hemodynamic balance in these regions is not impaired, the rational assumption to support this observation is AA having a very small diameter, that is being microvascular.[21] In the present study, a bilateral type D variation was observed only in one case.

In the present study, including 84 cases, AA is observed as 54.8% for type A, 17.9% for type B, 10.7% for type C, and 16.7% for type D in the right hemiface and 50% for type A, 28.6% for type B, 13.1% for type C, and 8.2% for type D in the left hemiface. Kim et al conducted a study on 57 facial halves of 30 cadavers. In their analysis of AA course variation, they found type A as 19.3%, type B as 31.6%, type C as 22.8% and type D as 26.3%. The AA originated from the FA as 50.9% of the facial halves (types A + B).[9] Mas et al examined 32 facial halves of 16 cadavers in which their classic angular type corresponded to our type B variation (25%), the nasal type to our type A variation (46.9%), and the alar type (12.5%) and labial type (15.6%) to our type C variation. The authors observed no type D variation.[10] Mas et al stated that FA ended symmetrically in 10 cadavers (62.5%).[10] Koh et al found that 54.5% (24/44) of FA had a symmetrical distribution.[22] In the present study, the FA ended symmetrically in 39 of 84 (46.4%) cases. Vasilic et al reported that AA did not end at a terminal branch of the FA in 28% of the facial halves.[23] Mas et al, in turn, reported that AA ended at the terminal branch of FA in all cases.[10] Koh et. al reported that FA ended at the AA in 50% (12/24), at the LNA in 45.8% (11/24), and at the inferior labial artery in 4.2% (1/24).[22] Different from anatomical terminology, Pınar et al described the several terminal types of FA as angular branch, nasal branch, alar, superior labial, and hypoplastic branches, and stated that the FA was asymmetrical in 32% of the 25 studied heads. They reported further that 22% of the FA facial halves ended at the angular branch, 60% at the nasal branch, 12% at the alar branch, 4% at the superior labial branch, and 2% at the hypoplastic branch.[24] Despite this study, some anatomy textbooks indicate that the FA is referred to as the AA after the division of the superior labial artery.[25] The findings of the present study resemble those of a typical anatomy textbook, although no detailed assessment could be made in the lateral nasal region as the size of the ultrasound probe and the nasal morphological structure prevented a full 360° orientation. Mas et al accepted that the FA ended as the AA, as in the typical textbooks, after dividing into the superior labial arterial branch. They defined the AA types as classic type, nasal type, alar type, and labial type based on their course.[10] Loukas et al examined 284 facial halves derived from 142 cadavers and made a detailed variation observation about distribution models classified into five types in the FA.[26] (A–E): type A (47.5%), the FA divides into the superior labial

TABLE 4 Relationship between body mass index and skin-FA depth and skin-bone depth

	Skin-FA depth at the origin of the mandible of right FA	Skin-mandible depth at the origin of the mandible of right FA	Skin-FA depth at the origin of the mandible of left FA	Skin-mandible depth at the origin of the mandible of left FA
BMİ				
r	0.712	0.661	0.743	0.724
P	<.001	<.001	<.001	<.001

Abbreviation: r, the correlation coefficient.

TABLE 5 Correlation between AA variations and skin-artery, skin-bone depths in the right hemiface

Right	A (n = 46) Mean ± SD (mm)	B (n = 15) Mean ± SD (mm)	C (n = 9) Mean ± SD (mm)	D (n = 14) Mean ± SD (mm)	*P*
Skin-FA depth at the origin of the mandible of right FA	6.26 ± 1.95	7.33 ± 2.65	6.46 ± 2.45	6.40 ± 1.26	.380
Skin-mandible depth at the origin of the mandible of right FA	9.69 ± 2.45	10.64 ± 3.16	10.31 ± 3.09	9.80 ± 1.91	.624
Skin-FA depth at right cheilion	7.96 ± 2.69	10.66 ± 3.57	8.80 ± 3.65	9.44 ± 2.39	**.019**
Skin-FA depth at right inferior nasal ala	9.14 ± 2.84	10.37 ± 3.44	9.28 ± 4.73	10.06 ± 2.75	.538
Skin-maxilla depth at right inferior nasal ala	14.89 ± 3.37	16.76 ± 4.39	14.88 ± 3.99	15.79 ± 2.53	.320

$P < 0.05$: statistical significance value.

TABLE 6 Correlation between AA variations and skin-artery, skin-bone depths in the left hemiface

Left	A (n = 42) Mean ± SD (mm)	B (n = 24) Mean ± SD (mm)	C (n = 11) Mean ± SD (mm)	D (n = 7) Mean ± SD (mm)	*P*
Skin-FA depth at the origin of the mandible of left FA	5.89 ± 2.04	6.53 ± 2.42	6.02 ± 2.66	6.03 ± 1.74	.736
Skin-mandible depth at the origin of the mandible of left FA	9.10 ± 2.76	9.77 ± 2.67	9.43 ± 3.72	8.89 ± 2.23	.794
Skin-FA depth at left cheilion	8.22 ± 2.35	8.83 ± 2.07	10.14 ± 2.10	9.79 ± 3.38	.069
Skin-FA depth at left inferior nasal ala	10.01 ± 3.33	10.83 ± 3.58	11.05 ± 2.71	11.54 ± 3.37	.548
Skin-maxilla depth at left inferior nasal ala	15.60 ± 4.14	17.26 ± 3.97	16.74 ± 2.57	18.40 ± 2.88	.182

and lateral nasal branches (then gives inferior and superior alar and ends as angular branch); type B (38.7%) is similar to type A, but the FA ends as the lateral nasal superior alar branch (no AA); in type C (8.4%), the FA ends as the superior labial branch; in type D (3.8%), the AA arises directly from the facial artery trunk rather than ending as a lateral nasal branch; and in type E (1.4%), the FA terminates as a primitive branch without giving any significant branch. The type A in the study by Loukas et al corresponds to the type A in the present study, while Types B and C are akin to types C and D in our study. Loukas et al did not examine the association between OA and AA. Type D in their study corresponds to type B in our study. We did not come across any examples of the type E in the study by Loukas et al Saban et al evaluated the AA on 40 live cases at the level of the piriform aperture using Doppler ultrasonography. Also, Saban et al examined the FA on 20 cadavers [13] and stated that the FA divided into terminal branches by advancing to the alar-facial fold through the medial upper lip after an oral commissure in 32 (80%) cases. This course was referred to as typical FA (type 1). The type A in the present study corresponds to type 1 in the study by Saban et al They demonstrated that FA extended to the cheek through the lateral NLF and divided into the lateral nasal and angular arteries in six (15%) cases. They reported that they considered this course to be

Skin-FA depth at right cheilion	Skin-FA depth at left cheilion	Skin-FA depth at right inferior nasal ala	Skin-maxilla depth at right inferior nasal ala	Skin-FA depth at left inferior nasal ala	Skin-maxilla depth at left inferior nasal ala
0.531	0.307	0.547	0.634	0.553	0.523
<.001	<.005	<.001	<.001	<.001	<.001

TABLE 7 Correlation between FA course variations and skin-artery, skin-bone depths in the right hemiface

Right	1 (n = 30) Mean ± SD (mm)	2 (n = 15) Mean ± SD (mm)	3 (n = 21) Mean ± SD (mm)	4 (n = 18) Mean ± SD (mm)	*P*
Skin-FA depth at the origin of the mandible of right FA	5.89 ± 1.59	7.69 ± 2.96	6.67 ± 2.09	6.31 ± 1.39	**.043**
Skin-mandible depth at the origin of the mandible of right FA	9.13 ± 1.99	11.09 ± 3.63	10.54 ± 2.58	9.66 ± 1.94	.058
Skin-FA depth at right cheilion	8.07 ± 2.34	10.83 ± 4.33	8.26 ± 2.95	8.86 ± 2.36	**.026**
Skin-FA depth at right inferior nasal ala	8.54 ± 2.27	11.10 ± 4.06	8.60 ± 3.15	10.94 ± 2.74	**.005**
Skin-maxilla depth at right inferior nasal ala	14.33 ± 2.44	17.37 ± 4.96	14.66 ± 3.76	16.27 ± 2.63	**.021**

P < 0.05: statistical significance value.

TABLE 8 Correlation between FA course variations and skin-artery, skin-bone depths in the left hemiface

Left	1 (n = 31) Mean ± SD (mm)	2 (n = 16) Mean ± SD (mm)	3 (n = 27) Mean ± SD (mm)	4 (n = 10) Mean ± SD (mm)	*P*
Skin-FA depth at the origin of the mandible of left FA	5.58 ± 1.66	7.36 ± 3.14	6.19 ± 2.05	5.47 ± 1.63	**.046**
Skin-mandible depth at the origin of the mandible of left FA	8.74 ± 2.28	10.58 ± 4.20	9.54 ± 2.34	8.47 ± 2.23	.130
Skin-FA depth at left cheilion	8.33 ± 2.41	11.08 ± 2.54	8.10 ± 1.83	8.30 ± 1.23	**.001**
Skin-FA depth at left inferior nasal ala	9.26 ± 3.15	13.60 ± 3.90	10.16 ± 2.38	10.37 ± 2.03	**.001**
Skin-maxilla depth at left inferior nasal ala	14.82 ± 4.19	19.28 ± 3.92	16.48 ± 2.99	16.95 ± 2.37	**.002**

P < 0.05: statistical significance value.

long (type 2) FA. Type B of our study corresponded to type 2 of the study by Saban et al, who reported that FA ended in the parasymphyseal region in two (5%) cases and referred to this as short (type 3) FA. Types C and D in the present study correspond to type 3 in the study by Saban et al They established that the other facial half contralaterally had type 1 FA.

In 2014, Yang et al reported that in 93.3% the branch of the FA proceeded around the NLF and was located 3.2 ± 4.5 mm and 13.5 ± 5.4 mm lateral to the nose alar and oral commissure, respectively. Also, the detoured branch stretched along the lower edge of the orbicularis oculi muscle.[27]

Mas et al measured the diameter of the lateral nasal branch as minimum 0.8 mm and maximum 1.4 mm, with an average of 1.0 mm.[10] Wu et al reported that the FA diameter to be approximately 2 mm in 12 cadaver samples, while the AA diameter was approximately 1 mm.[20] In the present study, the FA diameter was a minimum 0.8 mm and maximum 2.2 mm, with a mean of 1.56 ± 0.35 mm at the FA mandibular origin.

Wu et al reported that the FA extended into the nostril through cheilion just underneath the NLF in all samples from 12 cadavers [20] and stated that the FA, in general, was located in the layer inferior to the superficial musculoaponeurotic system (SMAS), which lies inferior to levator labii superioris and the levator labii superioris alaeque nasi. They further demonstrated that the FA was located in the subcutaneous plane in the NLF in four samples. Wu et al performed depth of the arterial structures, considering the SMAS as the origin, but made no quantitative depth analysis. The present study assessed the FA based on the body mass index (weight/height in meters), based on measurements made at the FA's mandibular origin, cheilion and nasal ala inferior levels. The distance from the upper wall of the FA to the subcutaneous area was measured in millimeters, which is a quantitative value. The skin-mandible distance at the FA's mandibular origin and the skin-maxilla distance at the inferior nasal ala were evaluated. The FA diameter at the FA's mandibular origin was also included in the measurements.

According to Wu et al, a deep injection into the periosteum in the nasal dorsum and the NLF is safer than the under-SMAS plane. That said, there is no absolutely safe region or route for filler injections due to the wide anastomoses between the facial arteries.[20] The present study investigated the average depth of that FA that runs

TABLE 9 Comparisons between skin-FA average depths and the statistical significance

	Between 2nd variation and 1st variation in the right hemiface	Between 2nd variation and 1st variation in the left hemiface	Between 2nd variation and 3rd variation in the left hemiface	Between the 2nd variation and the 4th variation in the left hemiface	Between 1st variation and 4th variation in the right hemiface
Origin of the mandible of FA	*P*:.027	*P*:.040			
Cheilion	*P*:.020	*P*:.001	*P*:.001	*P*:.011	
İnferior nasal ala	*P*:.038	*P*:.001	*P*:.003	*P*:.042	*P*:.039

with no right-left facial half distinction and the depth at which it runs at a statistical confidence interval of 95%. The average FA depth was 6.3 mm at the FA's mandibular origin, varying between 5.98 mm and 6.62 mm at a 95% confidence interval. The average FA depth was 8.78 mm at the cheilion and varied between 8.36 mm and 9.20 mm at a 95% confidence interval. The average FA depth was 10.02 mm at the nasal ala and varied from 9.52 mm to 10.51 mm at a 95% confidence interval. The minimum and maximum depths of the FA along its course suggest that its course may be highly superficial (2.5 mm at the mandibular origin, 3.7 mm at the cheilion and 3.7 mm at the nasal ala). It also suggests that the FA may follow a very deep course near the periosteum (15.0 mm at the mandibular origin, 18.7 mm at the cheilion and 23.5 mm at the nasal ala). We think there is no absolutely safe region or route for filler injections.

The present study established a statistically high-to-moderate linear correlation between body mass index, skin-facial artery depth, and skin-bone (mandible and maxilla) depth (Table 4). Increasing the body mass index increases the skin-FA and skin-bone distances. When the association between the AA variation, and the skin-fascial artery and skin-bone (mandible and maxilla) depths in the right and left facial halves was examined, the variation B in the average skin-FA depth at the cheilion in the right facial half was found to be localized deeper than variation A. That said, there was no statistical difference in the average depths of the AA course variations in all other measurements performed on the right and left facial halves. The common ground in our comments on the classification of the FA course in the right and left facial halves is that the FA running at the superior NLF (Type 2) was localized deeper.

An analysis of the association between the variation distribution of the AA and the course variation of the FA in both facial halves suggests the following implications: The type 1 variation usually presents with variation A (variation A in the right facial half, 70%; variation A in the left facial half, 71%). The type 2 variation usually presents with variations A and B (variations A + B in right facial half, 80%; variations A + B in the left facial half, 75.1%). The type 3 variation usually presents with variations A and B (variations A + B in the right facial half, 90.5%; variations A + B in the left facial half, 88.9%). The type 4 variation was not observed to have any significant associations with the AA variations.

Although it could not be proven with statistical data, Kim et al reported that variation B was observed to run further from the midline than variation A, based on the AA pattern. When the FA course of the cases with variation B based on AA patterns were examined regardless of the right and left facial halves, it was found that two (5.1%) were type I, 10 (25.6%) were type II, 22 (56.4%) were type III, and five (12.8%) were type IV. Variation type B, which was observed at rates of 17.9% and 28.6% in the right facial half and left facial half, respectively, usually traversed the NLF from the inferior to the superior or ran parallel with the superior NLF.

Kim HJ et al made a classification of the FA course based on the NLF, similar to the present study.[11] They found type 1, type 2, type 3, type 4 as 42.9%, 23.2%, 19.6%, 14.3% respectively. In the present study, type 1 was 35.7%, type 2 was 17.9%, type 3 was 25%, type 4

TABLE 10 The relationship between the distribution of variation of AA in the right hemiface and FA course variation

		Right FA course variation (1,2,3,4)				
		1	2	3	4	
		n (%)	n (%)	n (%)	n (%)	*P*
Right AA variation (A,B,C,D)	A	21 (70.0)	7 (46.7)	13 (61.9)	5 (27.8)	**.002**
	B	1 (3.3)	5 (33.3)	6 (28.6)	3 (16.7)	
	C	4 (13.3)	1 (6.7)	0 (0.0)	2 (11.1)	
	D	4 (13.3)	2 (13.3)	3 (27.3)	8 (44.4)	

$P < 0.05$: statistical significance value.

TABLE 11 The relationship between the distribution of variation of AA in the left hemiface and FA course variation

		Left FA course variation (1,2,3,4)				
		1	2	3	4	
		n (%)	n (%)	n (%)	n (%)	*P*
Left AA variation (A,B,C,D)	A	22 (71.0)	7 (43.8)	9 (33.3)	4 (40.0)	**.01**
	B	2 (6.5)	5 (31.3)	15 (55.6)	2 (20.0)	
	C	5 (16.1)	2 (12.5)	1 (3.7)	2 (20.0)	
	D	2 (6.5)	2 (12.5)	1 (3.7)	2 (20.0)	

$P < 0.05$: statistical significance value.

was 21.4% in the right facial half, and type 1 was 36.9%, type 2 was 19.1%, type 3 was 32.1%, and type 4 was 11.9% in the left facial half. An analysis of the course of the FA revealed types 1 and 2 to be less common in the Turkish population than in the Korean population, whereas type 3 is more common in the Turkish population which represents a Caucasian population.

Mass et al reported a limitation of their study being that the arterial mapping and classification of AA was based only on cadaver assessment and emphasized that findings comparative with computed tomographic angiography, digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and similar radiological techniques were needed.[10] Although literature contains several cadaver studies of the FA and AA, there has been no ultrasonography study to date making an anatomical assessment of AA. Saban et al examined the wings of the nose for nasal vascularity using ultrasonography.[13] There has been one cadaver study using computed tomography which is the available modality among the radiological modalities.[12] To the best of our knowledge, there has been no study to date of live cases using ultrasonography analyzing both AA variations and the course of the FA based on the NLF.

The present study has several limitations. The main limitation of this study is the lacking of a gold standard for comparison to other imaging techniques such as CT, MRA, DSA, or ex-vivo information. Anatomy of the face is strictly linked to the race. The study had been done only in Turkish population. This is an another limitation of this study. In our study, no detailed assessment could be made of the lateral nasal region due to the size of the ultrasound probe, and the nasal morphological structure did not permit a full 360° orientation. It is known that Doppler ultrasonographic examinations are adversely affected by emerging weak ultrasound signals when blood vessels are small and deeply located in soft tissue.[28] It is hoped that this situation will change with technological advances. The differences in the findings of the many studies may result from the current technological status of radiological systems, the sampling interval, racial differences, and confusion in the naming of the AA and in the definition of its course. Another reason for the inconsistencies in the rates and naming of the AA between studies may be related to a confusion on the terminological classification regarding the terminal naming of the FA in some studies.[25] As FA runs a parallel course to NLF, we thought that the depths of FA at the starting and the ending points of NLF could give us enough information about the depth of the FA through the NLF. However, our results must be interpreted with caution, since we did not performed additional measurements between these two points. This limitation in the study could be addressed in future research which may examine more landmarks along the NLF by dividing the NLF into several sites.

The subcutaneous plane, though frequently injected to achieve best cosmetic improvement, is the most high-risk location as the vasculature most commonly courses through this region. Injecting into a vessel is less likely when injecting deep directly on bone or very superficially in the dermis. However, especially in the most upper part of the NLFs, injecting deep directly on bone requires much more amount of filler to achieve good results, which can double the cost of the effective treatment, by causing a need for an additional syringe of filler. Injecting very superficially in the dermis is also not very operable to NLFs, since it can lead to lumps and bumps.

NLF filler injections are performed just under and a few millimeters medial depressed side of the fold to fill the NLF. The FA is not running at this side in type II course (FA is parallel and superior to the NLF) patients. Considering the course variation of the FA at

the NLF, we can safely perform the injections in only about %18 of the patients. When we consider the depth of the artery, FA depth was varied between 8.36 mm and 9.20 mm at the cheilion, between 9.52 mm and 10.51 mm at the nasal ala at a 95% confidence interval. Accordingly, superficial subcutaneous injections up to 8.36 mm is safe in 95% of the patients. However, the most superficial FA depth is measured as 3.7 mm in this study. As the thickness of the skin including the epidermis and the dermis in NLF is about 2 - 2,5 mm, and the most superficial FA depth is measured 3.7 mm in this study, the safe zone for the filler injections in such patients seems to be 1,2 to 1,7 mm subdermal in these patients. We may suggest that very superficial injections adjacent to the dermis for this reason, however precision of injections at this level, may not be always possible. Therefore, intraarterial injection risk reduction strategies should especially be applied when injecting to NLF, which includes aspiration (although a negative or positive aspiration cannot be totally relied upon), injecting small amounts at a time, continually moving the needle or cannula, slow low-pressure injection technique, observing the pain and skin changes of the patient during injections. The use of wide cannula to inject fillers into high-risk areas may also be a safer alternative to needles; however, intravascular injection can still occur albeit less commonly with cannula.

It is believed that a firm understanding of vascular anatomy can prevent the complications. However, according to our findings the expert mastery of vascular anatomy is not failsafe in the nasolabial area as vascular anatomy is highly variable and vascular events may still occur even in the hands of expert injectors. A recent study showed that the frequency of inadvertent intravascular injection is high, among very experienced injectors, supporting the findings of our study.[5]

5 | CONCLUSION

The present study classified the AA according to its origin, course, and end point and determined its course based on the NLF. The values with measured depths of the arterial and adjacent bone structures in certain localizations were compared with the body mass indexes of the cases. The findings of this study suggest that avoiding vessels in NLF is difficult because of the variability of human FA and AA vascular anatomy and there is no absolutely safe depth or region for nasolabial fold filler injections. These findings will contribute to better outcomes in cosmetic surgery and facial filler injections by allowing a better understanding of the anatomy of the AA and FA, in order to stimulate discussion for new filler injection strategies for this region.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

BT, TK, TİK, MAY: Project development, Data collection, Data analysis, Manuscript writing. GT, YB, ÜT, KE: Project development, Data analysis, Manuscript editing.

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