Review

Prevalence of Musculocutaneous Nerve Variations: Systematic Review and Meta-analysis

FELICE SIRICO,[1] * CLOTILDE CASTALDO,[1] VERONICA BAIOCCATO,[1] NASTASIA MARINO,[1] MARCELLO ZAPPIA,[2,3] STEFANIA MONTAGNANI,[1] FRANCA DI MEGLIO,[1] AND DARIA NURZYNSKA[1]

[1]*Department of Public Health, University of Naples "Federico II", 80131, Naples, Italy*
[2]*Department of Medicine and Health Sciences, University of Molise, 86100, Campobasso, Italy*
[3]*Department of Diagnostic Imaging, Varelli Institute, 80126, Naples, Italy*

We aimed to establish the prevalence of the musculocutaneous nerve (MCN) variations and the probability of the variation being pure or mixed in the same plexus. We applied the principles of evidence-based anatomy to find, appraise, and synthesize data through a meta-analysis of anatomical studies. The variations were grouped based on the presence and location of the communicating branch with the median nerve and the origin of branches to anterior arm muscles. Forty-three cadaveric studies met the inclusion criteria, providing data from 4124 plexuses. The overall pooled prevalence of plexuses with MCN variations was 20%. Based on the classification applied in our study, the pooled prevalence of variations was 17% in region 1A, 20% in region 1B, 36% in region 2 and 49% in region 3. Importantly, 64.58% of variations in region 1A and 74.14% of variations in region 1B were mixed, that is, associated with a variation in another region. The odds of finding another variation in the presence of a variation in region 2 or 3 were equal 0.37 and 0.52, respectively, demonstrating a significantly lower probability of finding mixed variations involving these regions, when compared with region 1A. Variations of the MCN are most common in the part distal to the exit from within or beneath the coracobrachialis muscle. Proximal variations are more often associated with another variation located along the nerve. These findings can assist health care professionals in the treatment of brachial plexus lesions. Clin. Anat. 9999:1–13, 2018.

Key words: musculocutaneous nerve; brachial plexus; anatomy; prevalence; meta-analysis

INTRODUCTION

The musculocutaneous nerve (MCN) is one of the main terminal branches of the brachial plexus. Typically, the MCN carries motor and sensory fibers from the C5, C6, and C7 segments of the spinal cord and arises from the lateral cord of the brachial plexus, which gives origin also to the lateral root of the median nerve (MN). The MCN supplies the muscles of the anterior compartment of the arm (the coracobrachialis, biceps brachii, and brachialis muscles) and the

*Correspondence to: Felice Sirico, Department of Public Health, University of Naples "Federico II", via S. Pansini 5 (bldg 20, room 207), 80131 Naples, Italy.
E-mail: sirico.felice@gmail.com

Franca Di Meglio and Daria Nurzynska are joint senior authors.

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skin on the lateral aspect of the forearm. Along its course in the arm, the MCN pierces the coracobrachialis muscle; distally, it descends between the biceps brachii and brachialis muscle; just below the elbow, it pierces the deep fascia lateral to the tendon of the biceps brachii and continues as the lateral cutaneous nerve of the forearm (Standring, 2008). This anatomical course exposes the nerve to lesion during trauma or surgery in the anterior compartment of the arm.

Anatomical studies of lower vertebrate embryos suggest that the MCN derives from the MN (Mahan and Spinner, 2016). Indeed, this developmental pattern, or its modification during the segregation of fibers into typical nerves, is evident while analyzing variations. The most common variation of the MCN is the presence of an anastomotic branch with the MN, reported with a frequency ranging from 12% to 36% (Le Minor, 1990; Venieratos and Anagnostopoulou, 1998; Choi et al., 2002). Other variations include the absence of the MCN (Sarkar and Saha, 2014) and an origin of the branch for the coracobrachialis muscle from the lateral cord (Bhanu and Sankar, 2012). Similarly, the level of penetration of the nerve into the coracobrachialis muscle is highly variable and, importantly, variably expressed, ranging from 51 to 83 mm from its origin (Macchi et al., 2007) or from 32 to 104 mm from the coracoid process (Ozturk et al., 2005). Frequently, the MCN does not pierce the muscle (Kervancioglu et al., 2011).

Variations in the MCN are common findings encountered during anatomical dissections. In clinical practice, however, these variations are silent until a lesion occurs. In brachial plexus damage, diagnosis can be difficult when clinical impairments are not in line with the typical distribution of plexus branches. Preventive investigations aimed at defining the presence of these variations in patients are ineffective. Although magnetic resonance imaging and medical ultrasound technique can define the exact course of the peripheral nerves, these techniques do not allow visualization of the motor branches arising from a nerve trunk. Similarly, electrophysiological studies, including electroneurography and needle electromyography, used to investigate the integrity of the peripheral nervous system structures in standard clinical practice, are rarely able to define the pattern of motor fiber distribution. Their presence can increase the risk of iatrogenic injury during treatment of the humeral fracture, coracoid process mobilization, or upper extremity regional anesthesia. Knowledge of the expected and actual branching pattern of the MCN would be useful in several clinical procedures, such as electrodiagnostic investigation of the peripheral nerve lesion (Sonck et al., 1991), treatment of spasticity of the elbow flexor muscles by injections of the neurolytic agents (Moon et al., 2012), or treatment of recurrent anterior shoulder instability. A recent meta-analysis of 45 studies of the Bristow-Latarjet shoulder stabilization has estimated that the rate of MCN injury in this procedure is 0.6% (Griesser et al., 2013).

Variations in the MCN were classified by Le Minor (Le Minor, 1990) into five types, numbered I through V. In type I, there is no communication between the MN and the MCN; in type II, the communication branch of the MCN joins the MN; in type III, the lateral root of the MN leaves the MCN after it gave off its muscular branches; in type IV, the MCN arises from the MN; finally, in type V, the MCN is absent and the branches to elbow flexors emerge from the MN. The classification by Venieratos (Venieratos and Anagnostopoulou, 1998) is based on the features that was neglected by Le Minor, specifically, the origin of the communicating branch with respect to the coracobrachialis muscle. Accordingly, it identifies type-I variation when the communicating branch is proximal to the point of entry into the muscle, type II when it is distal and type III when the MCN does not pierce the coracobrachialis muscle. Although frequently used, these classifications do not cover all variations encountered during anatomical dissections. Hence, many novel classifications have been suggested and employed in dissection studies (Kosugi et al. 1992; Choi et al. 2002; Loukas and Aqueelah, 2005; Uysal et al., 2009; Guerri-Guttenberg and Ingolotti, 2009; Maeda et al., 2009; Kaur and Singla, 2013; Leng et al., 2016; Hayashi et al., 2017), making it difficult to estimate the exact frequency of the encountered variations in the general population. Arguably, even the most precise and all-inclusive classifications tend to miss the point, which is not to simply classify the encountered variation in the plexus once it has been dissected. Above all, data emerging from plexus dissection and classification should be applicable in practice, for example providing a medical practitioner with the information on the most frequent location of variation and its possible association with other variations that might be encountered in a patient.

The aim of the present study was to review the available literature on MCN variations and pool data about the prevalence of variations through a meta-analysis. The patterns of MCN origin, course, and branching are variable and classifications proposed in the literature are highly heterogeneous, although detailed and complex. Therefore, for the purpose of our analysis, we grouped variations based on the presence and location of the MCN-MN communicating branch and the origin of the branches to the anterior arm compartment muscles. This allowed us to assess the effect of variation localization on the likelihood that variation was pure or associated with other variations along the same plexus. The latter information should be particularly valuable in planning and performing interventions on brachial plexus.

MATERIALS AND METHODS

In the present meta-analysis, we implemented the Checklist for Anatomical Reviews and Meta-Analyses (Yammine, 2014) and observed the later developed guidelines to conducting systematic reviews and meta-analysis of anatomical studies (Henry et al., 2016) to find, appraise, and synthesize data on MCN variations reported in literature. As none of the above-mentioned guides is accompanied by a reporting checklist to be included in the published meta-analysis, we submitted the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher et al., 2009), as the Supplementary Figure 1.

Search Strategy

The search strategy and study selection procedure followed the PRISMA guidelines (Moher et al., 2009). The following electronic databases were searched from incipit to March 2017: PubMed, Web of Science, Scopus, CINAHL, Medline and SpringerLink. The search process was performed using specific syntax rules for each database and combining the following terms with adequate Boolean operators: musculocutaneous nerve, variations, anomaly, absence, anastomosis, communications, median nerve, anatomy, morphology, structure. English language restriction was applied. Results were collected using a reference manager software. After duplicates were removed, the articles were screened for relevance based on their titles. The abstracts of the selected articles were then evaluated according to the inclusion and exclusion criteria for study selection. The full texts of all the included articles were collected and analyzed. A manual search was performed based on reference lists of the included articles to identify additional studies not obtained through the database search.

Criteria for Study Selection

Each study was independently evaluated by two authors (VB and NM). Disagreements during eligibility assessment were solved by a discussion with a third author (FS). Studies performed on cadavers were considered for inclusion, without age, sex or country of origin restriction. Only studies indicating the number of brachial plexuses and the number of the recorded MCN variations were included. Single-case reports were excluded from the analysis.

Data Extraction and Variation Classification

The extracted data included the name of the first author, year of publication, number of dissected plexuses, number of encountered variations and classification applied. For the purpose of this meta-analysis, we classified the documented variations into five groups, based on the pattern of the MCN origin and branching. In particular, the brachial plexus and the MCN were divided into three regions (Fig. 1) and the variations were allocated in three respective groups. Region 1 extended from the anterior rami of the cervical nerves to the point of division of the lateral cord into the MCN and the lateral root of the MN (group 1). Region 2 extended from the MCN origin to the exit from within or underneath the coracobrachialis muscle (group 2). Region 3 extended between the exit from within or underneath the coracobrachialis muscle and the distal tendon of the biceps brachii muscle (group 3). The variations within region 1 were further subdivided into two variants. In variant 1A, all the fibers of the lateral cord continued as the lateral root of the MN; thus the MCN was absent. In variant 1B, the lateral cord branching pattern was normal but some motor branches that typically arise from the MCN originated from the parts of the plexus proximal to the MCN (e.g., a branch for the coracobrachialis muscle arising directly from the lateral cord was present). The plexuses with variations in more than one of these regions were classified as mixed regions (group 4). Finally, the remaining plexuses were grouped under the heading "not defined" (group 5), if the included studies reported insufficient data to allocate the variation in at least one of the regions. Based on this model, we estimated the prevalence of each group in the entire sample and identified the most frequently variable region.

Risk of Bias Assessment

The quality and reliability of the included anatomical studies were assessed using AQUA tool (Henry et al., 2017). Five domains were evaluated, namely objectives and subject characteristics, study design, methodology characterization, descriptive anatomy, and reporting of results. Each domain was considered as either of low or high risk of bias, attributing high risk of bias if at least one of the signaling questions within each of the domains was answered negatively and low risk of bias if all the answers were positive. When doubts or differences arose between the reviewers, a consensus was reached. If a signaling question could not be answered owing to unreported or missing information, the risk of bias was judged as high.

Statistical Analysis

Data were analyzed in Stata software v.12 using the "metaprop" routine to aggregate prevalence estimates. The analysis was performed using a random effects model. The chi-square test and I-squared statistic were used to assess heterogeneity. I-squared statistic results were reported as percentages and an I^2 above 75% was considered as a relevant source of heterogeneity among included studies. The number of variations in each group was reported as percentage of the total number of brachial plexuses. In order to avoid the generation of a biased pooled estimate, we used the Freeman–Tukey double arcsine transformation, thus preventing the exclusion of studies with estimated proportion close or equal to one. Confidence intervals were calculated for individual studies.

A binomial logistic regression was performed to assess the effect of variation localization on the likelihood that variation itself could be pure (variation in only one region) or mixed (variations in two regions of the same plexus). Dependent variable was defined as dichotomous (pure variation OR mixed variation). Independent variable was the localization of variation (region 1A, region 1B, region 2, region 3).

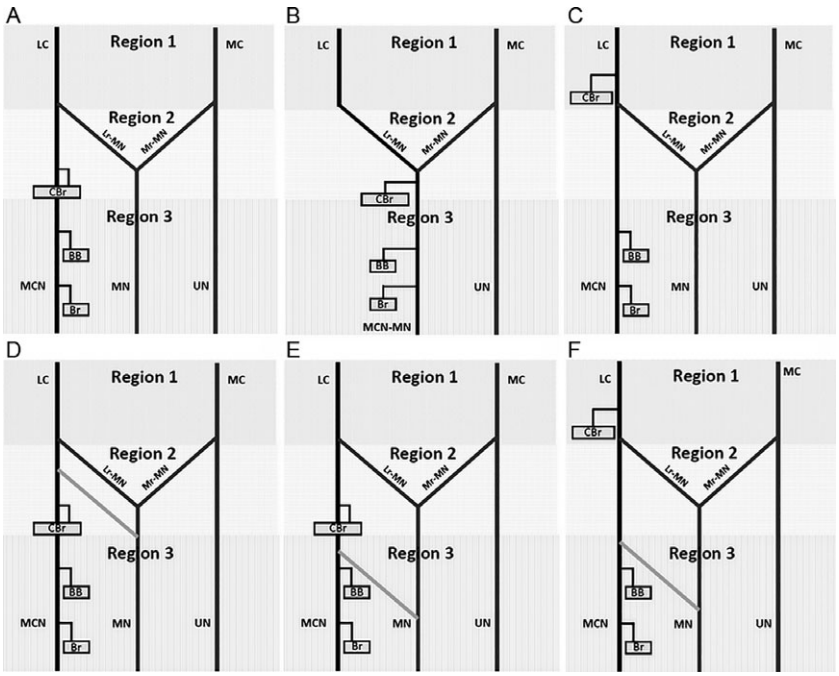

Fig. 1. Classification of MCN variations based on the region, with examples. **(A)** typical MCN origin and branching; **(B)** variation in region 1, variant 1A (absence of the MCN); **(C)** variation in region 1, variant 1B (branch to CBr from the lateral cord); **(D)** variation in region 2 (communicating branch between the MCN and MN); **(E)** variation in region 3 (communicating branch between the MCN and MN); **(F)** mixed variation (branch to CBr from the lateral cord in region 1 and communicating branch between the MCN and MN in region 3). BB, biceps brachii; Br, brachialis; CBr, coracobrachialis; LC, lateral cord; Lr-MN, lateral root of median nerve; MC, medial cord; MCN, musculocutaneous nerve; MN, median nerve; Mr-MN, medial root of median nerve; UN, ulnar nerve.

RESULTS

Study Selection

An adapted PRISMA flowchart summarizes the results of the study identification, screening, and eligibility evaluation (Fig. 2). Through database and reference search, 486 articles were identified. After removal of duplicates, 419 articles were excluded based on a two-step screening of a title and an abstract for relevance. Overall, 67 articles had their full-text retrieved and assessed for eligibility. Of these, 24 single-case reports were deemed unsuitable for prevalence estimation. As a result, 43 articles met the criteria and were included in the meta-analysis.

Characteristics of Included Studies

The characteristics of the included studies are summarized in Table 1. All included studies were performed on cadavers. Among 20 studies that specified the age of cadavers (fetus or adult), five studies (Uysal et al., 2009; Kervancioglu et al., 2011; Woźniak et al., 2012; Reis et al., 2014; Caetano et al., 2016) dissected fetuses, one study (Guerri-Guttenberg and Ingolotti, 2009) included both fetuses and adults, while 14 studies dissected only adult cadavers (Chiarapattanakom et al., 1998; Aktan et al., 2001; Choi et al., 2002; Beheiry, 2004; Loukas and Aqueelah, 2005; Pacha Vicente et al., 2005; Maheswari and Sadanandam, 2016; Pozo Kreilinger et al., 2007; Budhiraja et al., 2011; Sawant et al., 2012; Chaudhary et al., 2013; Ballesteros et al., 2015; Cambon-Binder and Leclercq, 2015; Leng et al., 2016). Only in eight studies, the variations were described together with information about the sex of individual cadavers in whom they were encountered. Three of those studies included only males (Aktan et al., 2001; Reis et al., 2014; Ballesteros et al., 2015) and five both males and females (Venieratos and Anagnostopoulou, 1998; Pozo Kreilinger et al., 2007; Chaudhary et al., 2013; Kaur and Singla, 2013; Master and Gupta, 2016). In total, those studies included three times as many male as female cadavers. The ethnicity of cadavers was explicitly stated only in five studies (Chauhan and Roy, 2002; Oluyemi et al., 2006; Bhattarai and Poudel, 2009; Kaur and Singla, 2013; Ballesteros et al., 2015). Similarly, laterality (one vs. two sides), side (left vs. right) of variations, and association with other anatomical variations (e.g., third head of the biceps

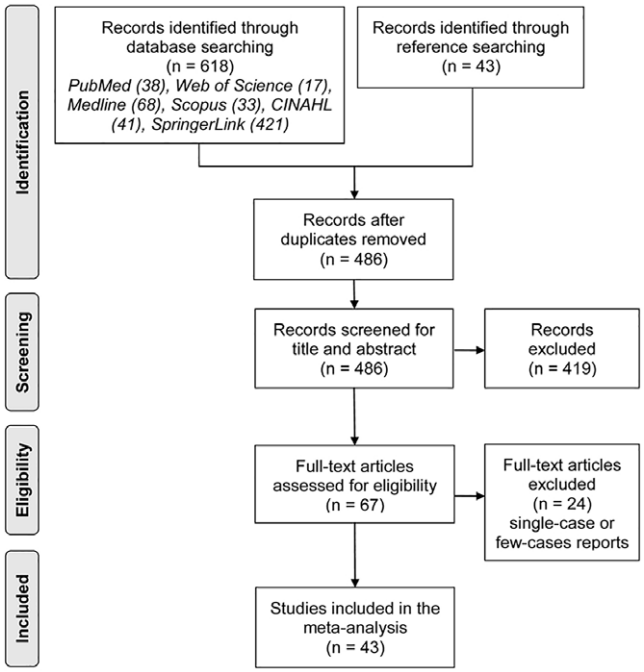

Fig. 2. PRISMA flowchart of the study selection process.

brachii) could not be considered due to incomplete data.

In the included studies, the classification originally proposed by Venieratos (Venieratos and Anagnostopoulou, 1998) was most frequently used (Prasada Rao and Chaudhary, 2001; Chauhan and Roy, 2002; Beheiry, 2004; Arora and Dingra, 2005; Loukas and Aqueelah, 2005; Maheswari and Sadanandam, 2016; Oluyemi et al., 2006; Chitra, 2007; Krishnamurthy et al., 2007; Uysal et al., 2009; Guerri-Guttenberg and Ingolotti, 2009; Budhiraja et al., 2011; Kervancioglu et al., 2011; Lokanadham and Subhadra Devi, 2012; Sawant et al., 2012; Balasubramanian and Rajanna, 2013; Chaudhary et al., 2013; Kaur and Singla, 2013; Kumar et al., 2013; Master and Gupta, 2016; Meenakshisundaram nad Govindarajan, 2016; Sonje et al., 2016), followed by the classification according to Le Minor (Le Minor, 1990; Chauhan and Roy, 2002; Beheiry, 2004; Arora and Dingra, 2005; Maheswari and Sadanandam, 2016; Oluyemi et al., 2006; Chitra, 2007; Krishnamurthy et al., 2007; Guerri-Guttenberg and Ingolotti, 2009; Lokanadham and Subhadra Devi, 2012; Sawant et al., 2012; Balasubramanian and Rajanna, 2013; Chaudhary et al., 2013; Dhar et al., 2013; Kaur and Singla, 2013; Kumar et al., 2013; Cambon-Binder and Leclercq, 2015; Sekhar and Sugavasi, 2015; Master and Gupta, 2016; Meenakshisundaram nad Govindarajan, 2016; Sonje et al., 2016). The authors of seven papers suggested their own methods of classification (Kosugi et al. 1992; Choi et al. 2002; Loukas and Aqueelah, 2005; Uysal et al., 2009; Maeda et al., 2009; Guerri-Guttenberg and Ingolotti, 2009; Kaur and Singla, 2013) and some of these were successively applied in other studies, while some authors did not attempt to classify the encountered variations of MCN (Yang et al., 1995; Chiarapattanakom et al., 1998; Aktan et al., 2001; Pacha Vicente et al., 2005; Channabasanagouda et al., 2013; Bhattarai and Poudel, 2009; Woźniak et al., 2012; Mavishettar and Iddalagave, 2013; Reis et al., 2014; Padur et al., 2016; Caetano et al., 2016).

Risk of Bias Assessment

The results of the risk of bias assessment of the individual studies included in our meta-analysis are reported in Table 2. All studies had a low risk of bias in domains two (study design) and three (methodology characterization) of evaluation according to the AQUA tool. However, all but one study (Ballesteros et al., 2015) posed a high risk of bias in our meta-analysis in domains one (objectives and study characteristics) and five (reporting of results), due to lack of demographic data and imprecise reporting of the variations. Most frequently, the missing information regarded the ethnicity of the dissected cadavers. When reporting the results, the variations were not associated with complete demographic data of the cadavers in whom they were encountered. This factor negatively influenced the possibility of subgroup analysis. High risk of bias in domain four (descriptive anatomy) was attributed to the studies in which the location of variation along the plexus or nerve course could not be determined based on the provided description. Indeed, those plexuses were excluded from our analysis of variation prevalence according to plexus regions.

In total, 4124 plexuses were included and 894 plexuses with MCN variations were identified. Based on the description reported in the included studies, we classified each variation as described above.

Meta-Analysis

The overall pooled prevalence of plexuses with MCN variations was 20% (95% CI, 15%–24%) (Fig. 3). Due to insufficient information about the exact location of the variations, it was not possible to classify 179 out of 894 plexuses with variations (20.02%). Based on the classification proposed in the present study, region 3 was most frequently involved, with variations in 411 plexuses (45.97%) reported only below the coracobrachialis muscle limit, followed by region 2, between the MCN origin and the lower limit of coracobrachialis, where variations were encountered in 177 plexuses (19.80%). Variations in region 1 were least frequent, with 34 plexuses (3.80%) presenting variant 1A (absence of the MCN) and 15 (1.68%) corresponding to variant 1B (branch to coracobrachialis arising proximally to the origin of the MCN). In 78 dissected plexuses (8.73%), the variations involved more than one region. The prevalence of different groups of classified plexuses (region 1, region 2, region 3, mixed

TABLE 1. Characteristics of the Studies Included in the Meta-Analysis

Study	Country	Cadaver number	Sex	Age	Plexus number	Variations total	Variations per region						Classification applied
							1A	1B	2	3	Mixed (regions)	Not defined	
Aktan et al., 2001	Turkey	24	24 M	Adult	48	5	0	0	5	0	0	0	none
Arora and Dingra, 2005	India	100	N/S	N/S	100	16	0	0	0	0	1 (1A + 2)	15	Le Minor, Venieratos
Balasubramanian and Rajanna, 2013	India	50	29 M, 21 F	N/S	50	17	2	0	0	1	0	14	Le Minor, Venieratos, Choi
Ballesteros et al., 2015	Colombia	53	53 M	Adult	106	21	0	0	0	21	0	0	Maeda
Beheiry, 2004	Egypt	30	N/S	Adult	60	4	0	0	1	2	1 (1A + 1B)	0	Le Minor, Venieratos, Choi
Bhattarai and Poudel, 2009	Nepal	16	N/S	N/S	32	2	0	0	1	1	0	0	none
Budhiraja et al., 2011	India	58	49 M, 9F	Adult	116	37	0	0	0	24	13 (1A + 1B)	0	Venieratos
Caetano et al., 2016	Brazil	20	13 M, 7 F	Fetus	40	10	0	0	0	0	0	10	none
Cambon-Binder and Leclercq, 2015	France	16	7 M, 9 F	Adult	16	4	1	0	0	3	0	0	Le Minor
Channabasanagouda et al., 2013	India	N/S	N/S	N/S	50	12	0	0	0	0	0	12	none
Chaudhary et al., 2013	India	30	28 M, 2 F	Adult	60	16	2	0	6	4	4 (1A + 1B)	0	Le Minor, Venieratos, Choi
Chauhan and Roy, 2002	India	200	N/S	N/S	400	1	0	0	0	1	0	0	Le Minor, Venieratos
Chiarapattanakom et al., 1998	Thailand	56	35 M, 21 F	Adult	112	18	0	0	0	9	0	9	none
Chitra, 2007	India	25	N/S	N/S	50	13	3	0	7	3	0	0	Le Minor, Venieratos, Choi
Choi et al., 2002	United Kingdom	138	66 M, 72 F	Adult	276	73	0	0	15	40	15 (1A + 3), 1 (2 + 3)	2	Choi
Dhar et al., 2013	India	21	N/S	N/S	42	1	0	0	0	0	1 (1A + 1B)	0	Le Minor
Guerri-Guttenberg and Ingolotti, 2009	Argentina	28	N/S	13 Adult, 15 Fetus								56	32
2	0	0	0	0	30	Le Minor, Kosugi, Venieratos, Choi, Loukas, Guerri-Guttenberg							
Kaur and Singla, 2013	India	30	28 M, 2 F	N/S	60	7	1	2	1	3	0	0	Le Minor, Venieratos, Kosugi, Kaur
Kervancioglu et al., 2011	Turkey	10	6 M, 4 F	Fetus	20	5	0	0	0	5	0	0	Venieratos
Kosugi et al., 1992	Japan	58	N/S	N/S	75	43	0	0	5	20	1 (1A + 1B)	17	Kosugi
Krishnamurthy et al., 2007	India	N/S	N/S	N/S	44	7	0	0	0	7	0	0	Le Minor, Venieratos, Choi
Kumar et al., 2013	India	N/S	N/S	N/S	50	14	0	0	11	2	0	1	Le Minor, Venieratos, Choi, Guerri-Guttenberg, Loukas
Leng et al., 2016	China	80	N/S	Adult	160	18	0	4	0	9	5 (1A + 3)	0	Kosugi, Choi, Leng
Lokanadham and Subhadra Devi, 2012	India	40	N/S	N/S	80	1	0	0	0	1	0	0	Le Minor, Venieratos
Loukas and Aqueelah, 2005	Netherlands Antilles	129	100 M, 29 F	Adult	258	119	0	0	54	44	10 (2 + 3)	11	Gegenbaur, Venieratos, Loukas
Maeda et al., 2009	Japan	227	N/S	N/S	453	193	0	0	0	175	18 (1A + 1B)	0	Hirasawa, Maeda

Maheswari and Sadanandam, 2016	India	N/S	N/S	Adult	60	4	0	0	1	3	0	0	Le Minor, Venieratos
Master and Gupta, 2016	India	28	20 M, 8F	N/S	56	12	2	0	0	10	0	0	Le Minor,Venieratos, Choi, Kaur
Mavishettar and Iddalagave, 2013	India	40	32 M, 8 F	N/S	40	17	5	5	0	0	0	7	none
Meenakshisundaram and Govindarajan, 2016	India	25	N/S	N/S	50	8	3	0	0	1	0	4	Le Minor, Venieratos
Oluyemi et al., 2006	Nigeria	24	23 M, 1 F	N/S	48	2	0	0	1	1	0	0	Le Minor, Venieratos
Pacha Vicente et al., 2005	Spain	43	N/S	Adult	46	13	0	0	0	0	3(1A + 3)	10	none
Padur et al., 2016	India	41	40 M, 1 F	N/S	82	4	2	1	1	0	0	0	none
Pozo Kreilinger et al., 2007	Spain	16	6 M, 10 F	Adult	32	4	0	0	0	3	1 (1B + 3)	0	Choi
Prasada Rao and Chaudhary, 2001	Zimbabwe	12	11 M, 1 F	N/S	24	2	2	0	0	0	0	0	Venieratos
Reis et al., 2014	Brazil	25	25 M	Fetus	50	11	0	0	5	0	0	6	none
Sawant et al., 2012	India	50	45 M, 5 F	Adult	100	30	8	0	22	0	0	0	Le Minor, Venieratos, Choi
Sekhar and Sugavasi, 2015	India	50	N/S	N/S	100	2	0	0	0	2	0	0	Le Minor
Sonje et al., 2016	India	40	35 M, 5 F	N/S	80	11	0	3	0	4	4 (1B + 3)	0	Le Minor, Venieratos
Uysal et al., 2009	Turkey	70	34 M, 36 F	Fetus	140	14	0	0	11	2	0	1	Choi, Venieratos, Uysal
Venieratos and Anagnostopoulou, 1998	Greece	79	35 M, 44 F	N/S	158	22	0	0	9	10	0	3	Venieratos
Woźniak et al., 2012	Poland	110	60 M, 50 F	Fetus	220	45	0	0	21	0	0	24	none
Yang et al., 1995	Singapore	24	N/S	N/S	24	4	1	0	0	0	0	3	none
TOTAL		2116	-	-	4124	894	34	15	177	41	178	179	-

F, female; M, male; N/S, not specified

TABLE 2. Risk of Bias Assessment According to Domains Reported in AQUA Tool (Henry et al., 2017)

	Risk of bias				
Study	Objectives and study characteristics	Study design	Methodology characterization	Descriptive anatomy	Reporting of results
Aktan et al., 2001	High	Low	Low	Low	High
Arora and Dingra, 2005	High	Low	Low	High	High
Balasubramanian and Rajanna, 2013	High	Low	Low	High	High
Ballesteros et al., 2015	Low	Low	Low	Low	Low
Beheiry, 2004	High	Low	Low	Low	High
Bhattarai and Poudel, 2009	High	Low	Low	Low	High
Budhiraja et al., 2011	High	Low	Low	Low	High
Caetano et al., 2016	High	Low	Low	High	High
Cambon-Binder and Leclercq, 2015	High	Low	Low	Low	High
Channabasanagouda et al., 2013	High	Low	Low	High	High
Chaudhary et al., 2013	High	Low	Low	Low	High
Chauhan and Roy, 2002	High	Low	Low	Low	High
Chiarapattanakom et al., 1998	High	Low	Low	High	High
Chitra, 2007	High	Low	Low	Low	High
Choi et al., 2002	High	Low	Low	High	High
Dhar et al., 2013	High	Low	Low	Low	High
Guerri-Guttenberg and Ingolotti, 2009	High	Low	Low	High	High
Kaur and Singla, 2013	High	Low	Low	Low	High
Kervancioglu et al., 2011	High	Low	Low	Low	High
Kosugi et al., 1992	High	Low	Low	High	High
Krishnamurthy et al., 2007	High	Low	Low	Low	High
Kumar et al., 2013	High	Low	Low	High	High
Leng et al., 2016	High	Low	Low	Low	High
Lokanadham and Subhadra Devi, 2012	High	Low	Low	Low	High
Loukas and Aqueelah, 2005	High	Low	Low	High	High
Maeda et al., 2009	High	Low	Low	Low	High
Maheswari and Sadanandam, 2016	High	Low	Low	Low	High
Master and Gupta, 2016	High	Low	Low	Low	High
Mavishettar and Iddalagave, 2013	High	Low	Low	High	High
Meenakshisundaram and Govindarajan, 2016	High	Low	Low	High	High
Oluyemi et al., 2006	High	Low	Low	Low	High
Pacha Vicente et al., 2005	High	Low	Low	High	High
Padur et al., 2016	High	Low	Low	Low	High
Pozo Kreilinger et al., 2007	High	Low	Low	Low	High
Prasada Rao and Chaudhary, 2001	High	Low	Low	Low	High
Reis et al., 2014	High	Low	Low	High	High
Sawant et al., 2012	High	Low	Low	Low	High
Sekhar and Sugavasi, 2015	High	Low	Low	Low	High
Sonje et al., 2016	High	Low	Low	Low	High
Uysal et al., 2009	High	Low	Low	High	High
Venieratos and Anagnostopoulou, 1998	High	Low	Low	High	High
Woźniak et al., 2012	High	Low	Low	High	High
Yang et al., 1995	High	Low	Low	High	High

region) is reported in Figure 4. When the presence of variation in one of regions was considered independently of whether it was pure or mixed, the pooled prevalence of variations was 17% (95% CI, 11%–24%) in region 1A, 20% (95% CI, 9%–32%) in region 1B, 36% (95% CI, 22%–51%) in region 2 and 49% (95% CI, 34%–63%) in region 3 (Fig. 5). Importantly, 62/96 variations (64.58%) in region 1A and 48/58 variations (74.14%) in region 1B were mixed. In contrast, variations in regions 2 and 3 were mostly pure (177/189, 93.56% and 411/450, 91.33%, respectively).

Next, we used the binomial logistic regression model to assess the effect of variation localization on

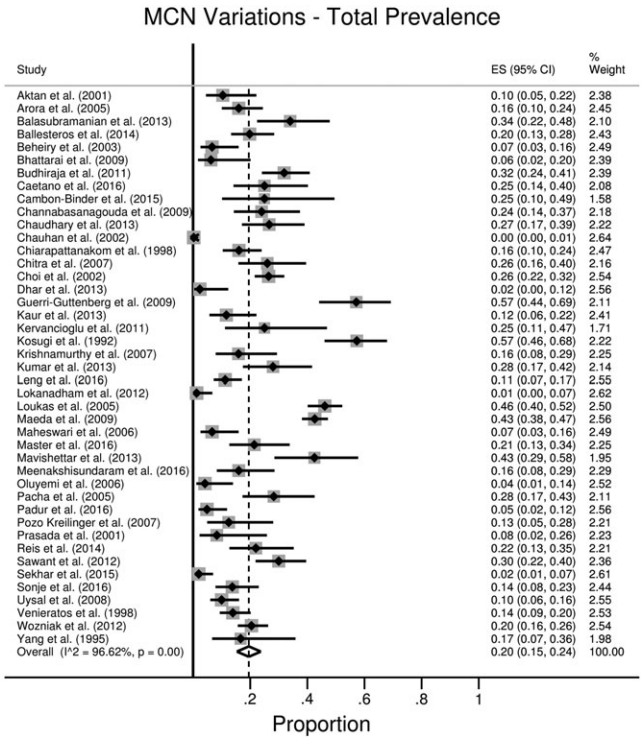

Fig. 3. Estimation of the overall pooled prevalence of plexuses with MCN variations.

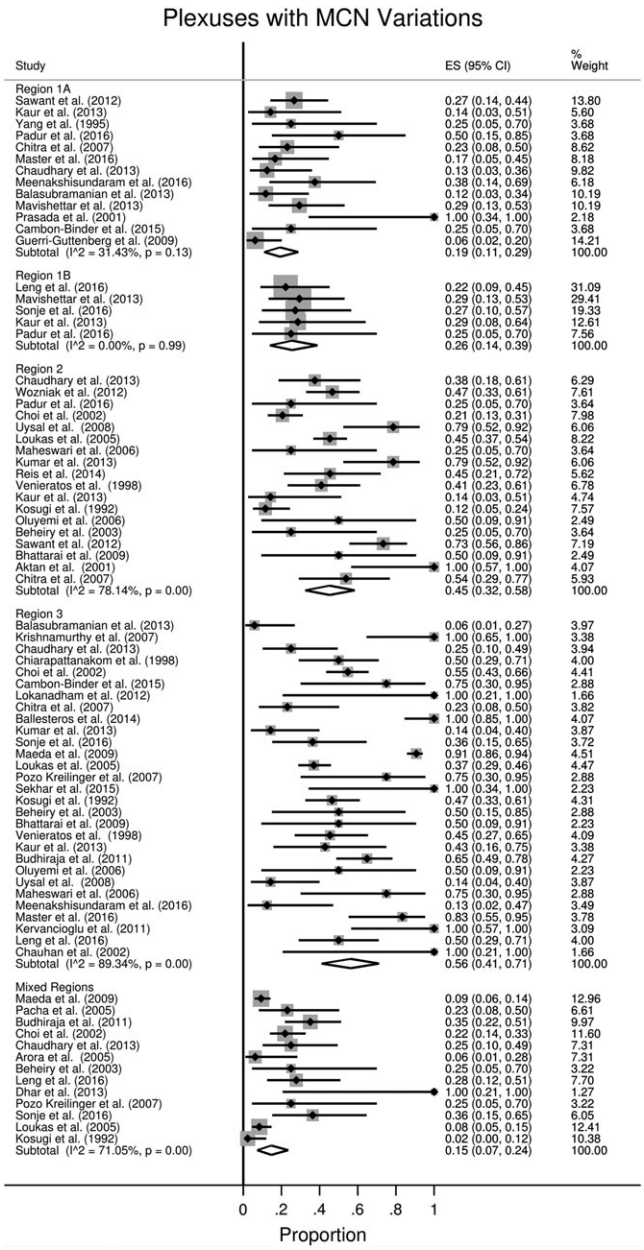

Fig. 4. Estimation of the pooled prevalence of different groups (region 1A, region 1B, region 2, region 3, mixed region) among classified plexuses with MCN variations.

the likelihood that variation was pure or mixed in our sample of 793 individual variations. Region 1A was considered a reference for comparison with other regions. Our logistic regression model was statistically significant, with $\chi^2(3) = 240.60$ and $p < 0.001$. In this model, the probability of finding another variation in the presence of a variation in region 1B was 57% higher (odds ratio [OR] = 1.57) than in the presence of a variation in region 1A (95% CI [0.76–3.23], P = 0.219); however, this difference was not statistically significant. A variation in region 2 or in region 3 was associated with an OR of 0.37 (95% CI [0.02–0.08], P < 0.001) or 0.52 (95% CI [0.03–0.09], P < 0.001), respectively, demonstrating significantly decreased probability of finding mixed variations involving these regions. The model explained 30.6% (Nagelkerke R2) of the variance in the type of variation (pure or mixed) and correctly classified 87.39% of cases. The sensitivity reached 67.31%, while the specificity reached 92.31%, with a positive and negative predictive value of 68.18% and 92.02%, respectively. Predicted probabilities of a variation in one of the regions being associated with a variation in another region are graphically reported in Figure 6.

Subgroup/Sensitivity Analysis

To investigate the possible sources of high heterogeneity observed in the present study, we attempted to perform subgroup analysis. As specified above, only 20 studies reported the age of cadavers (fetus or adult). Of those, one study included both fetus and adult cadavers, but the results were pooled; five studies included only fetus and 14 included only adult cadavers. We performed a subgroup analysis including only adult cadavers (Suppl. Fig. 2) and found that the prevalence of MCN variations (21% [95% CI, 14%–28%]) was not significantly different from the total prevalence in the pooled sample (20% [95% CI, 15%–24%]), with a complete overlap of the CIs. In few studies that specifically associated the variations

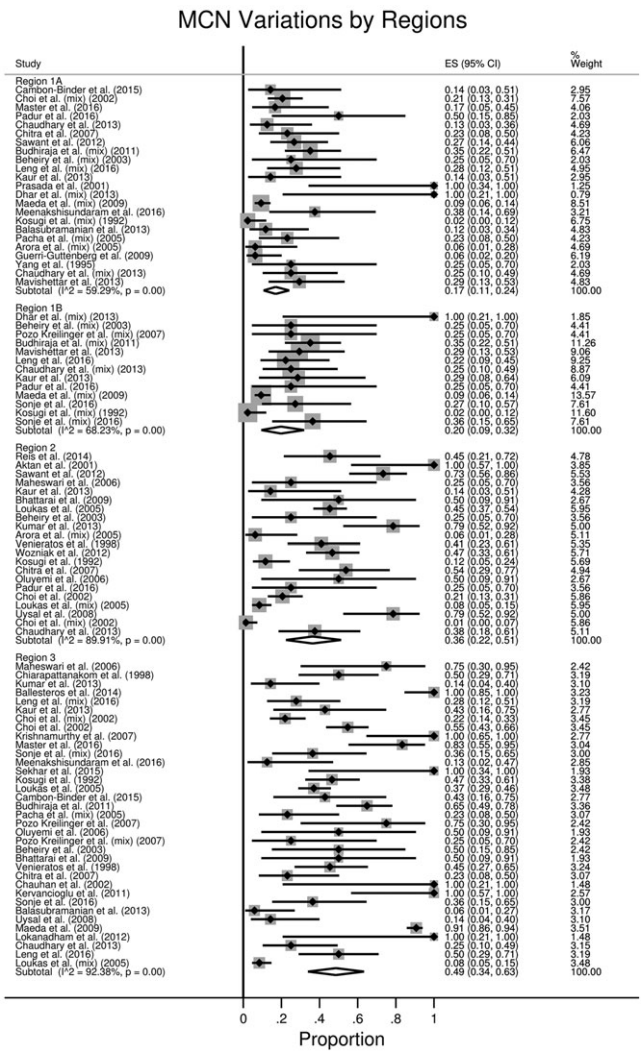

Fig. 5. Estimation of pooled prevalence of MCN variations in different regions (region 1A, region 1B, region 2, region 3) among classified plexuses.

with the sex of cadavers, the pooled sample size of male was three times as high as that of female cadavers, with the latter being <100. Hence, the sample was considered to be insufficient for comparison. Similarly, it was not possible to analyze the geographical distribution, laterality (one vs. two sides) and side (left vs. right) of the encountered variations.

When only the studies with a low risk of bias in the fourth domain of quality assessment, that is, descriptive anatomy, were included in the meta-analysis, the total prevalence of plexuses with MCN variations was 14% (95% CI, 9%–18%) (Suppl. Fig. 3). Noticeably, the heterogeneity was still high and not significantly different from that in the primary analysis. The excluded studies did not report sufficient information on variation localization, making it impossible to classify the encountered variations based on the region. Accordingly, those studies were not considered for

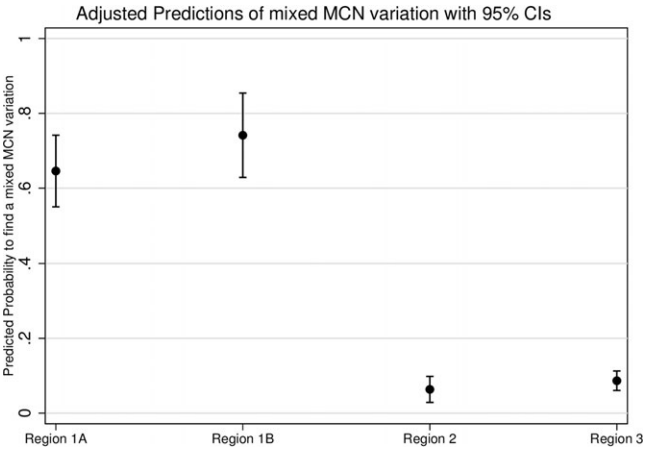

Fig. 6. Predicted probabilities of a variation in one of the regions being associated with a variation in other region in the same plexus.

and did not influence the results of our estimation of pooled prevalence of MCN variations in different regions.

DISCUSSION

The overall prevalence of plexuses with MCN variations when all the included studies were pooled for analysis was 20%. To the best of our knowledge, this is the first analysis that takes into consideration not only the number of plexuses with variations in the MCN origin or branching, but also the number of variations in the same plexus. Importantly, our meta-analysis demonstrated an important association between variation location and the probability of variation being pure or mixed, that is, accompanied by another variation along the same plexus. In particular, while most variations of type 1A or 1B in region 1 were mixed, the binomial logistic regression model demonstrated a significantly decreased probability of finding mixed variations involving regions 2 or 3.

The literature review shows that the variations in the communication between the MCN and MN have been classified in several ways. We are tempted to suggest that the presence and course of the communicating branches represent the most ambiguous aspect of the classification of the MCN variations. For example, the proximal branches from the MCN joining the MN in the upper third of the arm have been considered communicating branches of the MCN (Venieratos and Anagnostopoulou, 1998; Choi et al., 2002; Chitra, 2007) or a double lateral root of the MN, sometimes referred to as 'the third root of the median nerve' (Eglseder and Goldman, 1997; Saeed and Rufai, 2003). These differences may have contributed to the wide range of the prevalence of the MCN variations among studies (Guerri-Guttenberg and Ingolotti, 2009) and hindered any attempt at a meta-analysis without reconsidering the branching pattern and its classification. For the scope of our meta-analysis, we defined the limit between regions

1 and 2 distally to the division of the lateral cord of the brachial plexus in the MCN and the lateral root of the MN. Accordingly, the MCN-MN communication distal to that limit, hence in region 2, should be considered a communicating branch between the MCN and the MN, rather than a third root of the MN.

The presence of an anastomotic branch between the MCN and MN was often described in relation to the point of entrance of the MCN into the coracobrachialis muscle, according to Venieratos classification. In a study on 129 cadavers (Loukas and Aqueelah, 2005), 45% of the communications were proximal and 35% were distal to that point. However, the location of such anastomotic branch was not specified in the plexuses in which the MCN did not pierce the coracobrachialis muscle. This classification is, admittedly, simple and straightforward, but it tends to be of little significance when the aim of the study is the analysis of the location of the anastomotic branch between the MCN and MN. In particular, the exclusion of plexuses in which such a branch is present but the MCN does not pierce the coracobrachialis produces bias in the estimation of the prevalence of the communicating branch along the nerve.

Again, only the presence, and not the location, of the communicating branches were taken into consideration by the authors (Choi et al., 2002) who proposed their three patterns of variations based on the number of connecting branches or fusion of both nerves. Additionally, few reported cases in which the communication was formed by two or more branches from the MCN joining together before reaching the MN were classified as a distinct pattern. Interestingly, in those cases in which the MCN did not pierce the coracobrachialis muscle, the same authors observed that the communicating branch originated always distal to the point where it usually emerges from the muscle.

In the classification applied for the scope of our meta-analysis, the presence of the communicating branch between the MCN and the MN was considered with respect to its relation to the coracobrachialis muscle, and independent of the course of the nerve through or underneath the muscle (region 2, proximal, or region 3, distal to the exit of the MCN from within or underneath the coracobrachialis muscle). This approach permitted the inclusion of all plexuses and their variations in the analysis of the prevalence of variations along the plexus and the MCN. Indeed, it was region 3 where the variations were present most frequently, isolated in 411/793 plexuses and in association with a variation in another region in 39/793 plexuses, followed by region 2, in 177/793 and 12/793 plexuses, respectively.

Another reason behind the difficulty in comparing results between studies regards the absence of the MCN. As revealed by one analysis (Guerri-Guttenberg and Ingolotti, 2009), the fusion of the MCN with MN and the origin of the MCN from the MN could be classified by different authors into the same category. Other authors (Leng et al., 2016) classified the MCN as absent when the lateral cutaneous nerve of forearm and the branches to the brachialis and biceps brachii muscles originated from the MN, even if the branch to the coracobrachialis muscle was not identified; the MCN was present and classified as "mixed type" when the origin of the latter branch was from the lateral cord and all the other branches emerged from the MN. Adding to the confusion is the branch to the brachialis muscle; its motor fibers can emerge together with the sensory lateral cutaneous nerve. Again, the absence of the MCN was considered by the authors who described the origin of the branch to brachialis from the MN and its continuation as the lateral cutaneous nerve (Aydin et al., 2006; Sarkar and Saha, 2014); other authors suggested that the MCN should be considered to be absent only if the lateral cutaneous nerve of forearm emerging from the MN was purely sensory (Choi et al., 2002).

Yet another attempt at simplified MCN classification was based on the observed sequence of branches originating from the MCN (Hayashi et al., 2017). Unfortunately, these sensory and motor branches are not consistently reported in the brachial plexus descriptions in dissection studies and there is no agreement regarding the actual sequence of these branches along the nerve. Adding to these difficulties, some authors reported the origin of a branch to the nutrient canal of humerus from the MCN, but its actual localization is poorly defined and highly variable (Standring, 2008). Similarly, a branch to the glenohumeral joint is inconsistently reported. The branches to the biceps brachii and to the brachialis muscles can also differ in number and in morphology, as reported in one study (Yang et al., 1995) where a specific classification based only on these branches was suggested.

In the present meta-analysis and classification, all variations corresponding to the unusual origin of the motor branches were grouped in region 1 (variant 1A, if these branches arise from the MN, or variant 1B, if the motor branch to the coracobrachialis muscle arises from the lateral cord, proximal to its typical origin). These variations all indicate an unusual innervation of the flexor compartment of the arm, which should be taken into consideration during interventions along the MN (variant 1A) or at the apex of the axilla (variant 1B). Importantly, our analysis revealed that variations in these regions were typically mixed, possibly providing another clue as to the developmental pattern of fiber distribution along the brachial plexus. In clinical practice, these data could be useful in selecting cases that require a careful diagnostic approach and specific precautions in interventions on the brachial plexus.

Our study is not without limitations. First, data regarding 179 plexuses could not be included in the meta-analysis due to insufficient information on the localization of variations. This could cause underreporting bias and influence the accuracy of our inference about the variation prevalence. Second, a high heterogeneity was present and we were not able to explore all its possible sources due to the limited number of studies reporting sufficient demographic information and limited size of sample pooled from those that contained all necessary data. It is likely

that these limitations could have affected our results. There is no escaping the fact, however, that data are too often reported imprecisely and with insufficient detail. It strongly indicates a need for a more precise and standardized description of the observations and measurements in dissection studies. The inclusion of dissection studies on both adult and fetus cadavers proved to be reasonable, as we found that the prevalence of MCN variations in adult cadavers was not different from the total prevalence in the pooled sample. It is in agreement with the study by Guerri-Guttenberg and Ingolotti (2009), which compared the incidence of anatomical variations of the MCN in their sample of 15 fetus and 13 adult cadavers and found no significant difference between groups.

Finally, our approach to classification of variations based on their location could be argued to be unjustified. Indeed, the main problem that we identified analyzing the results of the included studies was related to the difference in the course of the MCN in relation to the coracobrachialis muscle. For one thing, the location of the variation was often indicated using the point where the MCN pierced the coracobrachialis muscle as a reference and the location of this point, as discussed in the main body of our paper, is variable. For the other, for the purpose of our meta-analysis, there was no reason for excluding also those cases in which the MCN did not pierce the muscle. Therefore, another reference point was needed to indicate the limit between the region 2 and 3 along the MCN. Our choice of extending this limit to the level at which the nerve emerges from underneath the muscle allowed us to include not only all the cases in which the MCN pierces the coracobrachialis muscle, but also all the cases in which the nerve does not pierce this muscle.

Notwithstanding the limitations of our study, the results confirm the high incidence of MCN variations in the arm. Importantly, the part of the MCN distal to the exit from within or beneath the coracobrachialis muscle is most commonly involved. Proximal variations are more often associated with another variation located along the nerve. These results can assist health care professionals in the diagnosis of and intervention for brachial plexus lesions.

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