Research, Society and Development, v. 11, n. 14, e16111435671, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i14.35671

Statistical allocation methods used in randomized controlled trials on bilateral carpal tunnel syndrome: an integrative literature review

Métodos de alocação estatística usados em ensaios clínicos randomizados sobre síndrome do túnel do carpo bilateral: uma revisão integrativa da literatura

Métodos de asignación estadística utilizados en ensayos controlados aleatorios sobre el síndrome del túnel carpiano bilateral: una revisión integrativa de la literatura

Received: 09/18/2022 | Revised: 10/10/2022 | Accepted: 10/13/2022 | Published: 10/24/2022

Sergio Murilo Georgeto
ORCID: https://orcid.org/0000-0002-7814-8780
University of Northern Paraná, Brazil
E-mail: georgetosm@gmail.com
Karen Barros Parron Fernandes
ORCID: https://orcid.org/0000-0002-1276-4900
University of Northern Paraná, Brazil
E-mail: karenparron@gmail.com
Eros de Oliveira Junior
ORCID: https://orcid.org/0000-0002-8421-0667
University of Northern Paraná, Brazil
E-mail: erosjunior@hotmail.com
Rodrigo Antônio Carvalho Andraus
ORCID: https://orcid.org/0000-0002-3849-0872
University of Northern Paraná, Brazil
E-mail: rodrigoandraus@gmail.com

Abstract
The objective of this review was to verify the available scientific evidence on allocation and concealment methods, and the statistical analyses used in randomized clinical trials (RCTs) on bilateral CTS. An integrative literature review was conducted, based on searches of databases for the period from 2014 to 2021. One-hundred-and-ten articles were found, of which 22 were considered eligible for inclusion. The statistical analyses methods used in the presence of bilateral pathologies was not clear in six (27.27%) cases and was inappropriate in another six (27.27%). A further five (22.72%) articles included only the most severely affected wrist for evaluation, while data from the right and left wrist were analyzed and described separately in four (18.18%) reports. Finally, only one (4.54%) RCT showed an adequate statistical approach. RCTs on clinical and surgical therapy of CTS do not use statistical models that include data repetition due to bilaterality when assessing outcomes.
Keywords: Carpal Tunnel Syndrome; Data analysis, Random allocation.

Resumo
O objetivo deste estudo foi verificar as evidências científicas disponíveis sobre métodos de alocação e as análises estatísticas utilizadas em ensaios clínicos randomizados (ECR's) sobre Síndrome do Túnel do Carpo (STC) bilateral. Foi realizada uma revisão integrativa da literatura, a partir de buscas em bases de dados no período de 2014 a 2021. Foram encontrados 110 artigos, dos quais 22 foram considerados elegíveis para inclusão. Os métodos de análise estatística utilizados na presença de patologias bilaterais não foram claros em seis (27,27%) casos e inadequados em outros seis (27,27%). Outros cinco (22,72%) artigos incluíram apenas o punho mais gravemente afetado para avaliação, enquanto os dados do punho direito e esquerdo foram analisados e descritos separadamente em quatro (18,18%) relatórios. Por fim, apenas um (4,54%) ECR apresentou abordagem estatística adequada. Os ECR's sobre terapia clínica e cirúrgica da STC não utilizam modelos estatísticos que incluam repetição de dados devido à bilateralidade na avaliação dos desfechos.
Palavras-chave: Síndrome do Túnel do Carpo; Análise de dados; Estudos randomizados.

Resumen
El objetivo de esta revisión fue verificar la evidencia científica disponible sobre los métodos de asignación y los análisis estadísticos utilizados en los ensayos clínicos aleatorios (ECA) sobre el STC bilateral. Se realizó una revisión integrativa de la literatura, basada en búsquedas en bases de datos para el período de 2014 a 2021. Se encontraron ciento diez artículos, de los cuales 22 se consideraron elegibles para inclusión. El método de análisis estadístico utilizado ante la presencia de patologías bilaterales no fue claro en seis (27,27%) casos y fue inadecuado en otros seis

(27,27%). Otros cinco artículos (22,72 %) incluyeron solo la muñeca más gravemente afectada para su evaluación, mientras que los datos de la muñeca derecha e izquierda se analizaron y describieron por separado en cuatro informes (18,18 %). Finalmente, solo un ECA (4,54%) mostró un enfoque estadístico adecuado. Los ECA sobre el tratamiento clínico y quirúrgico del STC no utilizan modelos estadísticos que incluyan la repetición de datos debido a la bilateralidad al evaluar los resultados.
Palabras clave: Síndrome del Túnel Carpiano; Análisis de datos; Métodos de asignación.

1. Introduction

Globally, carpal tunnel syndrome (CTS) is the most common median nerve compression neuropathy in the adult population and is the consequence of any pathological condition that causes a decrease in the cross-sectional area or an expansion of the components of the carpal tunnel (Alessia et al., 2020).

The incidence of CTS is three to four new cases in 1,000 people per year and has gradually increased in the last decade (Claire et al., 2018). This syndrome affects three times more women than men, predominantly affecting women between 30 and 40 years and men between 60 and 80 years, with bilateral involvement in 60% of cases (Tadjerbashi et al., 2019).

Multiple factors are responsible for the etiopathogenesis of CTS and some of the predisposing conditions are high impact physical activities, strenuous or repetitive manual work, constitutional factors, and clinical comorbidities (Chammas et al., 2014). However, given the impossibility of determining a causal agent, this syndrome is considered idiopathic (Ghasemi-Rad et al., 2014).

The diagnosis of CTS is performed by clinical or electromyographic criteria, and the combination of these two parameters has increased the diagnostic precision from 58% to 73% (Stevens, 1988). The degree of severity of this syndrome is defined by symptoms and signs (Becker et al., 2014) or by electromyography (EMG) (Padua et al., 1997). Stevens proposed a classification of severity (mild, moderate, and severe) based on EMG (Stevens, 1997).

Treatments for mild and moderate EMG findings may involve the use of an orthosis (Zinnuroglu et al., 2010) oral drugs (Huisstede et al., 2014), steroid infiltration (Carlson et al., 2010), photobiomodulation (Fusakul et al., 2014), therapeutic ultrasound therapy (Armagan et al., 2014), stretching exercises (Uribe-Quevedo et al., 2016), and myofascial release (Chang et al., 2014) or that of the treatments mentioned (Sim et al., 2018).

Surgery is indicated in cases of severe compression detected by EMG, cases that are unresponsive to clinical therapies, or worsening of both the clinical picture and the EMG parameters during clinical treatment (Uchiyama et al., 2010). Two surgical procedures are described in the literature: open surgery (OS) and endoscopic surgery (ES), with no evidence of the superiority of either technique (Thoma et al., 2004).

Clinical and surgical therapies reported in RCTs constitute an important parameter for the development of guidelines for clinical practice. In addition, RCTs are the basis for systematic reviews and meta-analyses used to consolidate the effectiveness of an intervention (Tarricone et al., 2016).

The literature presents guidelines for improving RCTs, thereby improving the validation of the indicated therapies. Some of the guidelines for treatment of CTS are those recommended by CONSORT (Consolidated Standards of Reporting Trials) (Moher et al., 2003), PEDro (Physiotherapy Evidence Database) (Shamseer et al., 2016) and Hooked on Evidence, organized by the American Physical Therapy Association (Moseley et al., 2009), which help researchers recognize the articles that present the best clinical evidence in specific rehabilitation studies (Manske & Lehecka, 2012). However, the guidelines proposed by CONSORT, PEDro, and Hooked on Evidence provide no recommendation on how to conduct RCTs or how to evaluate them in case of bilateral pathologies including bilateral CTS, although these conditions are common in the rehabilitation area (Shamseer et al., 2016).

When patients with bilateral pathologies are included in a study, there is an interrelationship between the outcome

measures. The effects of such information repetition result in bias and/or loss of efficiency in the statistical analyses, if statistical inference techniques that contemplate repeated measures are not adequately used (Bauer et al., 2013).

Page et al.30 performed a systematic search, with no time and language limits, about allocation and statistical methods in RCTs that included participants with bilateral CTS. After selecting 25 RCTs on clinical therapies, the authors concluded that most studies did not follow the standards recommended by the CONSORT. Moreover, most studies evaluated patients with bilateral involvement in an unsatisfactory way. Thus, they concluded that it was necessary to improve the allocation method and statistical analyses in studies including participants with bilateral CTS, in order to provide more reliable evidence to be used in clinical practice (Page et al., 2013).

Given this background, the present study evaluated the available scientific evidence on allocation methods and statistical analyses used in RCTs on bilateral CTS.

2. Materials and Methods

This is qualitative research of an applied nature with exploratory purposes. As for the procedures, it is bibliographic research using the integrative review method. This integrative literature review (IRL) was intended to gain understanding in a health guidelines-related problem, by incorporating purposes, defining concepts, reviewing evidence, and analyzing the methods used to propose guidelines for therapies for CTS from a content analysis of selected articles (Appendix). This IRL was guided by the phases of elaboration of the guiding question, definition of the search strategy in databases, article selection, information organization and classification, and presentation of the results found according Whittemore & Knafl (2005).

The PICO (patient, intervention, comparison, outcomes) strategy was used to construct the research question, where (P) represents wrists bilaterally affected by CTS and (I) represents allocation methods and statistical analysis. This review did not use (C) and (O) because they do not contemplate the answers sought by this study. Thus, the guiding question was defined as: "What scientific evidence is available on allocation and concealment methods, as well as on the statistical analyses used, in RCTs on CTS where the authors reported including participants with bilateral carpal in the sample?

The study searched for relevant published studies from January 2014 to February 2021, in the National Library of Medicine National Institutes of Health (PubMed), Web of Science, Scopus (Elsevier), and Science Direct databases. We used the following controlled descriptors selected from Medical Subject Headings (MeSH): Carpal Tunnel Syndrome, Random Allocation, Models Statistical, Randomized Controlled Trials. The uncontrolled descriptor (keyword) defined was bilateral Carpal Tunnel Syndrome.

Different search strategies were used, considering the peculiarities of each database, to ensure a wide-ranging search. The Boolean operators used were "OR" and "AND". Table 1 presents the search description in each database.

Table 1. Syntaxes used in the study search databases.

Databases	Search syntax
PubMed MEDLINE	"Carpal Tunnel Syndrome" [Title] AND ("Randomized controlled trial" OR "Random Allocation" OR "Statistical Model" or "Statistical Models")
Web of Science	TITLE: (Carpal Tunnel Syndrome) AND All fields: ("Randomized controlled trial" or "Random Allocation" OR "Statistical Model" or "Statistical Models")
Scopus	(TITLE-ABS-KEY ("Carpal Tunnel Syndrome") AND ALL ("Randomized controlled trial" OR "Random Allocation" OR "Statistical Model" OR "Statistical Models")
Science Direct	"Carpal Tunnel Syndrome" AND ("Randomized controlled trial" "Random Allocation" OR "Statistical Model" or "Statistical Models")

Source: Authors.

The inclusion criteria were: RCTs on the proposed topic, with full-text available, in Portuguese, Spanish, and English. Duplicate articles and secondary studies, such as theses, dissertations, literature reviews, systematic reviews, response letters, and editorials, were excluded.

After reading the title and abstract of the studies found, we retained only those that included the Boolean operators used in the search. Subsequently, after reading the entire article, the RCTs referring to clinical and surgical treatment, in which the authors reported the presence of participants with bilateral CTS in their sample, and which had been published in journals whose editors declared that they followed the CONSORT recommendations were maintained. The analyses were conducted by two independent researchers, and a third researcher was involved in case of disagreement. Summary tables were used to describe the information collected, using quantities and percentages for each characteristic of interest, and highlighting points of greater conceptual relevance.

3. Results

The literature search identified 110 studies, including 33 articles in PubMed, nine articles in Science Direct, 42 studies in Scopus, and 26 in the Web of Science. Of these, 40 were excluded due to duplication. In addition, 35 articles were excluded by title and abstract, and 13 more articles were excluded after full-text reading, leaving 22 articles on bilateral CTS (Table 2). The exclusion criteria for screening by the title and abstract, and for screening by the full article, were the absence of the required information for this review. Figure 1 shows the flow of selection of primary studies included in the integrative review according to the databases.

Table 2. Articles selected for the study.

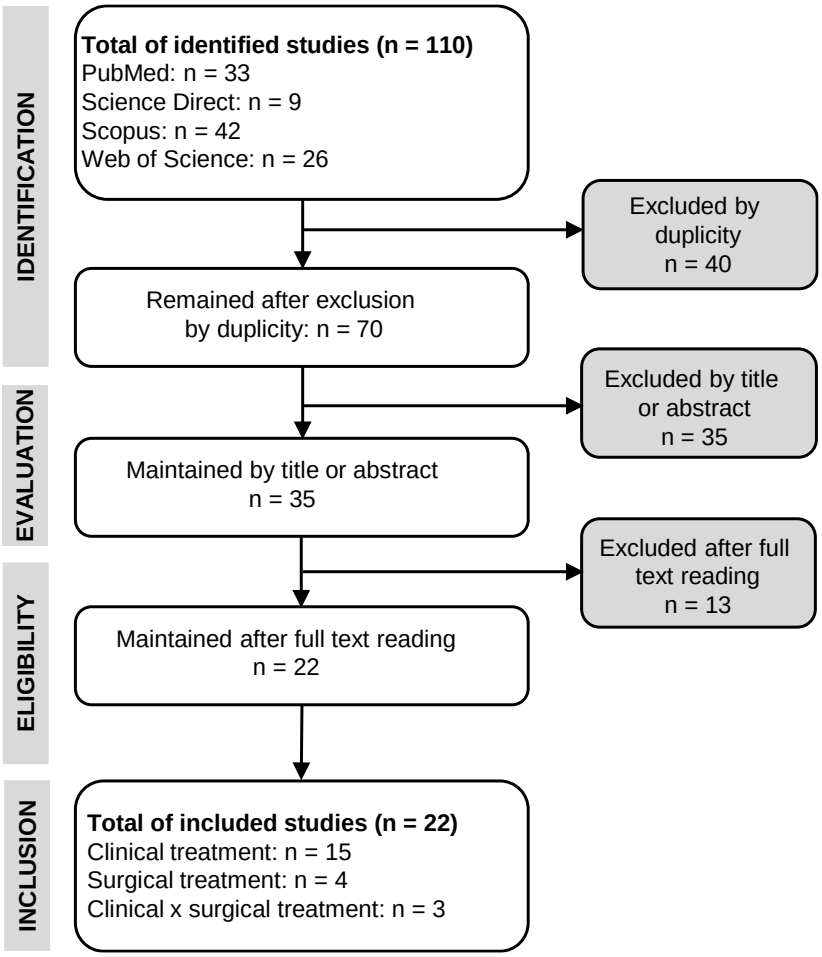
Title of the article	Author/ Year	Country
Immediate and durable clinical improvement in the non-operated hand after contralateral surgery for patients with bilateral carpal tunnel syndrome	Unno et al., 2014	Switzerland
Low-level laser therapy with a wrist splint to treat carpal tunnel syndrome: A double-blinded randomized controlled trial	Fusakul et al., 2014	Thailand
Prospective, randomized evaluation of endoscopic versus open carpal tunnel release in bilateral carpal tunnel syndrome	Michelotti et al.,2014	USA
Comparative effectiveness of ultrasound and paraffin therapy in patients with carpal tunnel syndrome: a randomized trial	Chang et al, 2014	Taiwan
Manual physical therapy versus surgery for carpal tunnel syndrome: A Randomized parallel-group trial	Fernández-de-las Peñas et al., 2015	Spain
Comparison of short-term clinical and electrophysiological outcomes of local steroid injection and surgical decompression in the treatment of carpal tunnel syndrome	Guarcay et. al. 2015	Turkey
Study to assess outcome after open and closed carpal tunnel decompression	Akhtar et al, 2015	USA and UK
The effectiveness of radial extracorporeal shock wave for treatment of carpal tunnel syndrome: A randomized clinical trial	Raissi et al., 2016	Iran
Mechanical wrist traction as a non-invasive treatment for carpal tunnel syndrome: A randomized controlled trial	Meems et al., 2017	Netherlands
The Val158Met polymorphism of the catechol-O-methyltransference gene is not associated with long-term treatment outcomes in carpal tunnel syndrome: A randomized clinical trial	Fernandez-de-las-Peñas et al., 2018	Spain
Intra-individual evaluation of results between open and endoscopic release in bilateral carpal tunnel syndrome	Fernandes et. al. 2018	Brazil
Short-term clinical outcome of orthosis alone vs combination of orthosis, nerve, and tendon gliding exercises and ultrasound therapy for treatment of carpal tunnel syndrome	Sim et. al. 2018	Malaysia

Comparison of Carpastretch® with splint in non-surgical treatment of carpal tunnel: A randomized open label study	Malshikare et al, 2018	India
Efficacy of manual therapy including neurodynamic techniques for the treatment of carpal tunnel syndrome: A randomized controlled trial	Wolny et. al, 2018	Poland
The assessment of acupuncture and exercise therapy in patients with carpal tunnel syndrome: Randomized cinical trial	Salehi et al., 2019	Iran
The long-term effect of neurodynamics vs exercise therapy on pain and function in people with carpal tunnel syndrome: A randomized parallel-group clinical trial	Hamzeh et al, 2019	Jordan
The comparison of the effectiveness between different doses of local methylprednisolone injection versus triamcinolone in carpal tunnel	Karimzadeh et al., 2019	Iran
Efficacy of manual therapy including neurodynamic techniques for the treatment of carpal tunnel syndrome: A randomized controlled trial	Wolny et. al, 2018	Poland
The assessment of acupuncture and exercise therapy in patients with carpal tunnel syndrome: Randomized cinical trial	Salehi et al., 2019	Iran
The long-term effect of neurodynamics vs exercise therapy on pain and function in people with carpal tunnel syndrome: A randomized parallel-group clinical trial	Hamzeh et al, 2019	Jordan
The comparison of the effectiveness between different doses of local methylprednisolone injection versus triamcinolone in carpal tunnel syndrome: A double-blind clinical trial	Karimzadeh et al., 2019	Iran
Effect of sensory relearning on sensory and motor functions of the hand in patients with carpal tunnel syndrome: A randomized controlled clinical trial	Elbalawy et al., 2019	Egypt
Acupuncture plus night splint for quality of life and disability in patients with carpal tunnel syndrome: A randomized controlled trial	Tezel et al, 2019	Turkey
Volume matters in ultrasound-guided perineural dextrose injection for carpal tunnel syndrome: A randomized, double-blinded, three-arm trial	Lin et al., 2020	Taiwan
Efficacy of platelet-rich plasma as an adjuvant to surgical carpal ligament release: prospective, randomized controlled clinical trial	Trull-Ahuir et al, 2020	Spain
Comparison of ultrasound-guided local ozone (O2-O3) injection versus corticosteroid injection in patients with mild to moderate carpal tunnel syndrome	Forogh et al. 2021	Iran

Source: Authors.

The 22 studies finally included were divided into periods: seven studies published between 2014 and 2015; two articles from 2016 to 2017; nine studies from 2018 to 2019; and three publications between 2020 and 2021. The total number of patients was 1,892, of which 717 participants had bilateral CTS. The sample size was calculated in 11 articles, the generation of a sequence for group allocation was described in 17 studies, and the concealment method used during allocation was reported in 16 studies. In 14 papers, participants were allocated by wrist. Only one article reported using appropriate statistical analysis to deal with bilateral wrist involvement. Table 3 shows these findings.

Figure 1. Flowchart of the selection of studies included in the integrative review, according to the databases searched.



Source: Authors.

Table 3. Description of the studies included in the IRL as for the characteristics of interest.

Characteristics of interest	n (%)									
Year of Publication	2014–2015		2016-2017		2018-2019		2020-2021		Total	
RCT including people with bilateral CTS	7	(31.8%)	2	(9.1%)	10	(45.5%)	3	(13.6%)	22	-
Participants	895	(47.3%)	221	(11.7%)	643	(34.0%)	133	(7.0%)	1892	-
Participants with bilateral CTS	368	(51.3%)	118	(16.5%)	206	(28.7%)	25	(3.5%)	717	(37.9%)
Defended the sample size	3	(27.3%)	0	(0.0%)	5	(45.5%)	3	(27.3%)	11	(50.0%)
Reporting random sequence generation method used	5	(29.4%)	2	(11.8%)	7	(41.2%)	3	(17.6%)	17	(77.3%)
Reporting allocation concealment method used	4	(25.0%)	2	(12.5%)	7	(43.8%)	3	(18.8%)	16	(72.7%)
Reporting method used in allocate wrists	6	(42.9%)	0	(0.0%)	5	(35.7%)	3	(21.4%)	14	(63.6%)
Reporting appropriate statistical analysis to deal with bilateral involvement	1	(100.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(4.5%)

Source: Authors.

Of the 22 RCTs selected, only two publications (9.1%) exclusively focused on bilateral carpi, while 17 articles (77.3%) did not explain the process of allocations of participants with bilateral carpi. In terms of treatment, in one article

(4.5%), participants with bilateral CTS underwent the same type of treatment in both wrists, and the average of the results were used to assess the outcomes. In another two studies (9.1%), only one hand was treated or operated, while the other side was disregarded in the presentation of the results. Table 4 shows these findings.

Table 4. Methods used for allocation of participants with bilateral carpus and reporting methods for the treatment used in these participants in the 22 RCTs evaluated.

Bilateral carpal allocation type/treatment report	Quantity	Percentage %
All were bilateral	2	9,1
Did not mention was done bilaterally	17	77,3
Bilateral sides received the same treatment, determining an average	1	4,5
One hand treated or operated	2	9,1%

Source: Authors.

Analysis of the studies' statistical approaches showed that, in six (27.3%) publications, the description of the statistical analysis did not clarify whether the model used was adequate. In other six (27.3%) studies, the statistical analysis was inappropriate. Despite bilaterality, only the most severely affected wrist was included in five (22.7%) studies; four (18.2%) studies analyzed and presented the results of the right and left wrists separately; and only one (4.5%) study used a mixed-effect analysis considering the examinations performed on both wrists for some participants. Table 5 shows these results.

Table 5. Proportion of the 22 clinical trials that included participants with bilateral carpal tunnel syndrome that used each of the following statistical analyses to deal with bilateral involvement.

Statistical analysis used to deal with bilateral involvement	Quantity/Percentage %
Unclear whether appropriate statistical analysis was used	6 (27.3)
Inappropriate statistical analysis used	6 (27.3)
Only the more severe of the two wrists was included in the analyses	5 (22.3)
Data for affected left and right wrists were analyzed and reported separately (only done for some outcomes)	4 (18.2)
Mixed-effect model, considering that the examination were performed on both wrists for some participants (only done for some outcomes)	1 (4.5)

Source: Authors.

4. Discussion

In order to answer the study question, only RCTs were selected, since their results present a higher level of evidence (Hopewell et al., 2007). Although the inclusion of articles with lower levels of methodological rigor, that is, literature that has not been formally published (gray literature) is a common practice, it is not recommended in studies that address health interventions (Egger et al., 2003).

The present study found that some RCTs of CTS, when reporting their results of both clinical and surgical therapies, failed because they did not follow the quality guidelines recommended by CONSORT (Shamseer et al., 2016), PEDro (Shiwa et al., 2017), and Hooked on Evidence (Moseley et al., 2009). The method used in the generation of the random sequence and a description of how allocation concealment was conducted was absent from a significant portion of the studies, with the former occurring in 22.7% and the latter in 27.3% of the included studies. Page *et al*. (2013) reported that 64% of the RCTs made no

mention of the method used for generating the random sequence, and 86% did not describe the allocation concealment mode (Page et al., 2013). The selection bias caused by a lack of random sequence generation and its adequate concealment impacted the validity of the causal inference (Smith & VanderWeele, 2019).

The present study demonstrated that failures in the inclusion of participants with bilateral CTS are related to three situations: a lack of specification of how the allocation of bilateral cases was made; bilateral wrists were treated using the same approach, with an average between the results reported; and consideration of only one of the hands for both treatment and for analysis of the study results. Padua *et al*. (2005) described similar failures when analyzing high-quality RCTs (Padua et al., 2005).

Likewise, a lack of rigor in the sample size evaluation was found in 50% of the RCTs, either by not mentioning how the number of participants was defined or by not demonstrating the calculations for its justification, potentially compromising the results obtained (Rodrigues et al., 2017). The inclusion of bilateral patients as if they were two independent cases artificially increased the total number of the sample, increasing the risk of incurring a type I error or false-positive (Song et al., 2009).

Studies should use statistical methods that consider the dependence between the wrists, due to bilaterality, when evaluating bilateral pathologies (Sauerland et al., 2003). Interdependent measures do not allow consideration of continuous or categorical characteristics between groups as independent. Therefore, it is not appropriate to use traditional tests, such as the *t*-test, chi-square test, analysis of variance, the Kruskal–Wallis, and the Mann–Whitney tests, which generate overestimated results (Winters et al., 2010).

The same person's hands can be compared using paired tests, such as the paired *t*-test and the Wilcoxon test for paired samples, and in the case of binary variables, the use of the McNemar test is appropriate. The unpaired version of these tests do not consider the effects of bilaterality, therefore they should not be used (Ali & Bhaskar, 2016). On the other hand, effects on a different scale must be considered when comparing some characteristics of the individual and their hands. Therefore, the most appropriate method in this case is the use of an analysis with mixed-effects models (Bauer et al., 2013).

Other options present a wide range of statistical analyses, addressing the different facets arising from the bilaterality of data to report the results of a therapy in patients with bilateral CTS. Some of these analyses are regression models (Ali & Bhaskar, 2016), generalized estimating equations (GEE) (Zeger & Liang, 1992) and multilevel modeling analysis (Diez-Roux, 2000). The GEE allows grouping of the results of both hands and comparison of the models, considering the correlations between the observations of each person, while the multilevel model assesses the data at different levels of variability, not being restricted to normality in its distribution, making a link between dependent observations incorporating the characteristics of bilaterality, and adjusting for both random-and mixed-effects, thus being indicated for the analysis of intra-individual measures.

5. Conclusion

When patients with bilateral pathologies are included in a study, there is an interrelationship between the outcome measures. The effects of such information repetition result in bias and/or loss of efficiency in the statistical analyses, if statistical inference techniques that contemplate repeated measures are not adequately used. The current guidelines provide no recommendation on how to conduct randomized controlled trials (RCTs) or how to evaluate them in case of bilateral carpus pathologies, including bilateral carpal tunnel syndrome (CTS), although these conditions are common in the rehabilitation area. Given this background, the present study evaluated the available scientific evidence on allocation methods and statistical analyses used in RCTs on bilateral CTS. The methodological problems resulting from not considering the presence of bilateral carpi when performing random allocation and concealment, and the use of statistical analyses that do not consider the

repetition of data due to bilaterality, have typically been neglected in RCTs on this topic, which can negatively impact the results.

Thus, in conclusion, in this analysis of RCTs on CTS, we found inadequacies in the analyses of subjects with bilateral CTS. RCTs published to date have typically not adequately indicated their allocation and concealment methods and have not following established guidelines for RCTs. Moreover, RCTs on bilateral CTS have not used statistical analyses that consider the interdependence of data due to bilaterality. These drawbacks negatively impacting the results of these trials. In the case of bilateral pathologies, it is necessary to establish recommendations that can guide researchers to use statistical analyses that take the interdependence of data caused by bilaterality into consideration, to raise the level of scientific evidence in the studies, in order to support clinical practice appropriately.

The study had some limitations. First, the electronic search was conducted in restricted databases, which may have resulted in the non-inclusion of some studies. Second, the scarcity of articles containing only samples with bilateral carpi, restricted the evaluations of the methodologies used in these cases (Tadjerbashi et al., 2019).

The high incidence of this syndrome in developed and developing countries, and the negative impact of this disease (Burton et al., 2018), both in terms of the physical limitation imposed and the economic cost of its treatment, justify the relevance of this study, and confirm the necessity of adjustments in future RCTs on bilateral CTS proposing therapeutic measures, to ensure robust results (Milone et al., 2019).

References

Alessia, G., Dix, O., Asem, S., Mala, T., & Hassan, A. (2020). Carpal Tunnel Syndrome: *A Review of Literature*. Cureus, 12(3).

Ali, Z., & Bhaskar, S. B. (2016). Basic statistical tools in research and data analysis. *Indian J Anaesth*, 60(9), 662-669. https://doi.org/10.4103/0019-5049.190623

Armagan, O., Bakilan, F., Ozgen, M., Mehmetoglu, O., & Oner, S. (2014). Effects of placebo-controlled continuous and pulsed ultrasound treatments on carpal tunnel syndrome: a randomized trial. *Clinics*, 69(8), 524-528.

Bauer, D. J., Gottfredson, N. C., Dean, D., & Zucker, R. A. (2013). Analyzing repeated measures data on individuals nested within groups: Accounting for dynamic group effects. *Psychological Methods*, 18(1), 1-30.

Becker, J., Scalco, R. S., Pietroski, F., Celli, L. F. S., & Gomes, I. (2014). Is carpal tunnel syndrome a slow, chronic, progressive nerve entrapment? *Clinical Neurophysiology*, 125(3), 642-646. http://www.clinph-journal.com/article/S1388-2457(13)01005-5/abstract

Burton, C. L., Chen, Y., Chesterton, L. S., & van der Windt, D. A. (2018). Trends in the prevalence, incidence and surgical management of carpal tunnel syndrome between 1993 and 2013: an observational analysis of UK primary care records. *BMJ open*, 8(6), e020166.

Carlson, H., Colbert, A., Frydl, J., Arnall, E., Elliot, M., & Carlson, N. (2010). Current options for nonsurgical management of carpal tunnel syndrome. *International journal of clinical rheumatology*, 5(1), 129.

Chammas, M., Boretto, J., Burmann, L. M., Ramos, R. M., Neto, F. S., & Silva, J. B. (2014). Carpal tunnel syndrome – Part II (treatment). *Revista Brasileira de Ortopedia (English Edition)*, 49(5), 437-445. https://doi.org/https://doi.org/10.1016/j.rboe.2014.08.002

Chang, Y., Hsieh, S., Horng, Y., Chen, H., Lee, K., & Horng, Y. (2014). Comparative effectiveness of ultrasound and paraffin therapy in patients with carpal tunnel syndrome: a randomized trial [Comparative Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. *BMC musculoskeletal disorders*, 15, 399. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/210/CN-01112210/frame.html

Claire, L. B., Ying, C., Linda, S. C., & A van der Windt, D. (2018). Trends in the prevalence, incidence and surgical management of carpal tunnel syndrome between 1993 and 2013: an observational analysis of UK primary care records. *BMJ open*, 8. https://doi.org/10.1136/

Diez-Roux, A. V. (2000). Multilevel analysis in public health research. *Annual review of public health*, 21(1), 171-192.

Egger, M., Juni, P., Bartlett, C., Holenstein, F., & Sterne, J. (2003). How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? *Empirical study. Health Technol Assess*, 7(1), 1-76.

Fusakul, Y., Aranyavalai, T., Saensri, P., & Thiengwittayaporn, S. (2014). Low-level laser therapy with a wrist splint to treat carpal tunnel syndrome: a double-blinded randomized controlled trial. *Lasers in medical science*, 29(3), 1279-1287.

Ghasemi-Rad, M., Nosair, E., Vegh, A., Mohammadi, A., Akkad, A., Lesha, E., Mohammadi, M. H., Sayed, D., Davarian, A., Maleki-Miyandoab, T., & Hasan, A. (2014). A handy review of carpal tunnel syndrome: From anatomy to diagnosis and treatment. *World J Radiol*, 6(6), 284-300. https://doi.org/10.4329/wjr.v6.i6.284

Hopewell, S., McDonald, S., Clarke, M. J., & Egger, M. (2007). Grey literature in meta-analyses of randomized trials of health care interventions. *Cochrane Database of Systematic Reviews*(2).

Huisstede, B. M., Fridén, J., Coert, J. H., Hoogvliet, P., & Group, E. H. (2014). Carpal tunnel syndrome: hand surgeons, hand therapists, and physical medicine and rehabilitation physicians agree on a multidisciplinary treatment guideline—results from the European HANDGUIDE Study. *Archives of physical medicine and rehabilitation*, 95(12), 2253-2263.

Manske, R. C., & Lehecka, B. (2012). Evidence–based medicine/practice in sports physical therapy. *International journal of sports physical therapy*, 7(5), 461.

Milone, M. T., Karim, A., Klifto, C. S., & Capo, J. T. (2019). Analysis of expected costs of carpal tunnel syndrome treatment strategies. *Hand*, 14(3), 317-323.
Moher, D., Schulz, K. F., Altman, D. G., & Group, C. (2003). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Clinical oral investigations*, 7(1), 2-7.

Moseley, A. M., Sherrington, C., Elkins, M. R., Herbert, R. D., & Maher, C. G. (2009). Indexing of randomised controlled trials of physiotherapy interventions: a comparison of AMED, CENTRAL, CINAHL, EMBASE, hooked on evidence, PEDro, PsycINFO and PubMed. *Physiotherapy*, 95(3), 151-156.

Padua, L., Lo Monaco, M., Padua, R., Gregori, B., & Tonali, P. (1997). Neurophysiological classification of carpal tunnel syndrome: assessment of 600 symptomatic hands. *Ital J Neurol Sci*, 18(3), 145-150.

Padua, L., Pasqualetti, P., & Rosenbaum, R. (2005). One patient, two carpal tunnels: statistical and clinical analysis—by hand or by patient? *Clinical Neurophysiology*, 2(116), 241-243.

Page, M. J., O'Connor, D., Pitt, V., & Massy-Westropp, N. (2013). Therapeutic ultrasound for carpal tunnel syndrome. *Cochrane Database Syst Rev*(3), Cd009601. https://doi.org/10.1002/14651858.CD009601.pub2

Rodrigues, C. F. d. S., Lima, F. J. C. d., & Barbosa, F. T. (2017). Importância do uso adequado da estatística básica nas pesquisas clínicas. *Revista brasileira de anestesiologia*, 67(6), 619-625.

Sauerland, S., Lefering, R., Bayer-Sandow, T., Brüser, P., & Neugebauer, E. (2003). Fingers, hands or patients? The concept of independent observations. *Journal of hand surgery*, 28(2), 102-105.

Shamseer, L., Hopewell, S., Altman, D. G., Moher, D., & Schulz, K. F. (2016). Update on the endorsement of CONSORT by high impact factor journals: a survey of journal "Instructions to Authors" in 2014. *Trials*, 17(1), 301.

Shiwa, S. R., Costa, L. O. P., de Lima Moser, A. D., de Carvalho Aguiar, I., & de Oliveira, L. V. F. (2017). PEDro: a base de dados de evidências em fisioterapia. *Fisioterapia em Movimento*, 24(3).

Sim, S. E., Gunasagaran, J., Goh, K. J., & Ahmad, T. S. (2018). Short-term clinical outcome of orthosis alone vs combination of orthosis, nerve, and tendon gliding exercises and ultrasound therapy for treatment of carpal tunnel syndrome. J *Hand* Ther. https://doi.org/10.1016/j.jht.2018.01.004

Smith, L. H., & VanderWeele, T. J. (2019). Bounding bias due to selection. *Epidemiology (Cambridge, Mass.)*, 30(4), 509.

Song, J. W., Haas, A., & Chung, K. C. (2009). Applications of statistical tests in hand surgery. *The Journal of hand surgery*, 34(10), 1872-1881.

Stevens, J. C. (1997). AAEM minimonograph 26: The electrodiagnosis of carpal tunnel syndrome [Review]. *Muscle and Nerve*, 20(12), 1477-1486. https://doi.org/10.1002/(SICI)1097-4598(199712)20:12<1477::AID-MUS1>3.0.CO;2-5

Stevens, J. S., S: Beard, CM: O'Fallon, WM: Kurland, LT. (1988). Carpal tunnel syndrome in Rochester, Minnesota, 1961 to 1980. *Neurology*, 38(1), 134-134.

Tadjerbashi, K., Åkesson, A., & Atroshi, I. (2019). Incidence of referred carpal tunnel syndrome and carpal tunnel release surgery in the general population: increase over time and regional variations. *Journal of Orthopaedic Surgery*, 27(1), 2309499019825572.

Tarricone, R., Boscolo, P. R., & Armeni, P. (2016). What type of clinical evidence is needed to assess medical devices? *European Respiratory Review*, 25(141), 259-265.

Thoma, A., Veltri, K., Haines, T., & Duku, E. (2004). A meta-analysis of randomized controlled trials comparing endoscopic and open carpal tunnel decompression. *Plastic and reconstructive surgery*, 114(5), 1137-1146.

Uchiyama, S., Itsubo, T., Nakamura, K., Kato, H., Yasutomi, T., & Momose, T. (2010). Current concepts of carpal tunnel syndrome: pathophysiology, treatment, and evaluation. *Journal of Orthopaedic Science*, 15(1), 1-13. http://link.springer.com/article/10.1007%2Fs00776-009-1416-x

Uribe-Quevedo, A., Ortiz, S., Rojas, D., & Kapralos, B. (2016). Hand tracking as a tool to quantify carpal tunnel syndrome preventive exercises. *2016 7th International Conference on Information, Intelligence, Systems & Applications (IISA)*,

Whittemore, R., & Knafl, K. (2005). The integrative review: updated methodology. *Journal of Advanced Nursing*, 52(5), 546-553.

Winters, R., Winters, A., & Amedee, R. G. (2010). Statistics: a brief overview. *Ochsner Journal*, 10(3), 213-216.

Zeger, S. L., & Liang, K. Y. (1992). An overview of methods for the analysis of longitudinal data. *Statistics in medicine*, 11(14-15), 1825-1839.

Zinnuroglu, M., Baspinar, M., & Beyazova, M. (2010). Carpal lock and the volar-supporting orthosis in mild and moderate carpal tunnel syndrome. *American journal of physical medicine & rehabilitation*, 89(9), 759-764.