



Characteristics of five-phase acupoints from data mining of randomized controlled clinical trials followed by multidimensional scaling

Seoyoung Lee^a, Yeonhee Ryu^b, Hi-Joon Park^a, In-Seon Lee^{a,*}, Younbyoung Chae^{a,*}

^a Department of Science in Korean Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea

^b KM Fundamental Research Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea

ARTICLE INFO

Article history:

Received 2 August 2021

Revised 6 December 2021

Accepted 9 December 2021

Available online 22 December 2021

Keywords:

Acupoint indication

Clinical trials

Clustering

Data mining

Multidimensional scaling

ABSTRACT

Background: An unbiased assessment of clinical outcomes may provide greater insight into the characteristics of individual acupoints. In this study, we used machine-learning methods to examine clinical trial data for diseases treated using prescribed five-phase acupoint patterns.

Methods: We performed a search of acupuncture treatment regimens used in randomized controlled trials included in the Cochrane Database of Systematic Reviews. The frequencies of 60 five-phase acupoints were calculated based on 421 clinical trials on 30 diseases. The characteristics of prescribed five-phase acupoints were further analyzed using multidimensional scaling and K-means clustering.

Results: Among the five-phase acupoints, stream and sea acupoints were the most widely used, with well, spring, and river acupoints less common. Multidimensional scaling and cluster analysis revealed that the LR3, ST36, GB34, BL60, KI3, LI11, and HT7 acupoints exhibited distinct characteristics based on distances representing the similarity between acupoint indications.

Conclusions: The results suggest that stream and sea acupoints exhibit distinct characteristics compared to the other acupoints. Such data-driven approaches will improve our understanding of five-phase acupoints and facilitate the establishment of new models of analysis and educational resources for major acupoint characteristics.

© 2021 Korea Institute of Oriental Medicine. Published by Elsevier B.V.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

1. Introduction

A wide variety of sources, ranging from neuroanatomy to the meridian theory of traditional East Asian medicine are considered when choosing the appropriate combinations of acupoints to use for a given indication.^{1, 2} Indeed, these various characteristics are blended in acupuncture prescriptions, and the main characteristics of prescribed acupoints can be used to classify acupoints, such as the twelve meridians.^{3, 4} Five-phase acupoints, also known as five-shu acupoints, are defined as a series of acupoints (well, spring, stream, river, and sea) along each meridian that are located below the elbow and knee areas in the limb extremities. These five-phase acupoints have long been regarded as the primary acupoints for most therapies, with records of their use spanning from clas-

sic medical textbooks through the present.⁵ For instance, in Saam acupuncture in Korea, specific principles have been developed using combinations of five-phase acupoints based on the five-phase theory⁶⁻⁸; however, there have been few investigations into the use of these five-phase acupoints in clinical trials.

Data-mining methods have revealed the relationships between acupoints and diseases by analyzing the prescribed acupoints originally outlined in classic medical textbooks.^{4, 9} Additional acupoints indications have also been revealed based on the relationships between individual acupoints and diseases found in clinical trials listed in the Cochrane Database of Systematic Reviews (CDSR).¹⁰ A subsequent analysis of the same database found that commonly used acupoints, most of which were five-phase acupoints, have been used to treat various pain conditions.^{11, 12} Hierarchical cluster analysis demonstrated that the spatial pattern of each meridian's indication was similar to the route of the corresponding meridian.⁹ Although these studies have demonstrated the use and indications of acupoints and meridians, the similarity (relatedness) or differences among the characteristics of selected acupoints have

* Corresponding authors at: Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul, Republic of Korea.

E-mail addresses: inseon.lee@khu.ac.kr (I.-S. Lee), ybchae@khu.ac.kr (Y. Chae).

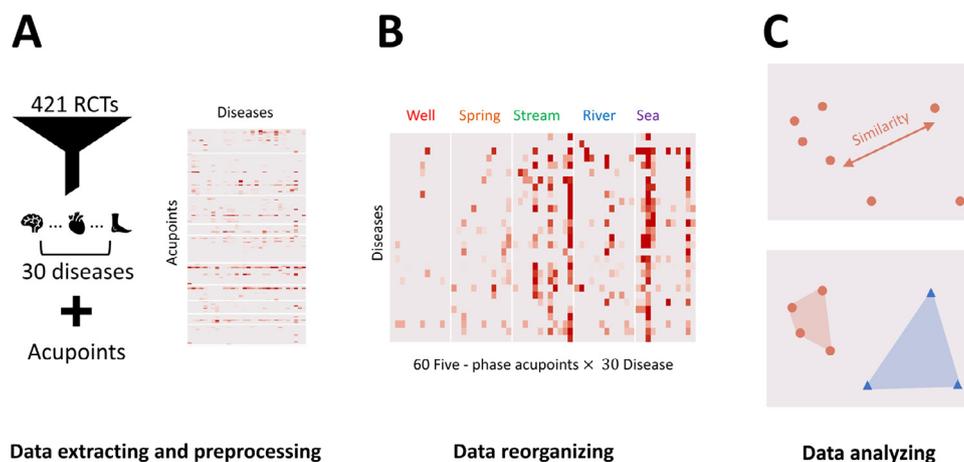


Fig. 1. Data extraction, analysis, and visualization. (A) Data extracting and preprocessing. Data were extracted from the Cochrane Database of Systematic Reviews. Acupoint data were collected from 421 randomized controlled trials of 30 diseases. The frequency of acupoint use for each disease was calculated by dividing the number of studies using a certain acupoint for the disease by the sum of all acupoints used for that disease. The usage frequencies of the 361 acupoints for all 30 diseases were listed in a 361×30 matrix (Acusynth). (B) Data reorganizing. Of the 361 total acupoints, 60 five-phase acupoints were extracted from the Acusynth database and clustered based on their labeled five-phase properties. (C) Data analyzing and visualization. Using multidimensional scaling (MDS), the acupoints were visualized based on their similarity to one another. Additional K-means clustering was conducted based on the MDS results.

never been studied. For example, the co-occurrence of two acupoints in a clinical trial does not mean that the acupoints have similar characteristics or there is a clear reason to choose these acupoints. Multidimensional scaling (MDS) can be used to reduce the dimensionality of the dataset and help visualize the intrinsic properties of individual acupoints based on their similarity to one another.¹³ Therefore, it is expected that we can use MDS to explore how five-phase acupoints are selected across different conditions. Such an approach will allow us to characterize each of the five-phase acupoints, which until now have been chosen based on theoretical principles, based on the relationships between the acupoints and diseases.

In this study, we aimed to identify the selection patterns and properties of five-phase acupoints used in clinical trials. Data were analyzed using MDS to visualize the similarities among 60 acupoints on a single map. Cluster analysis of acupoint selection patterns was applied to identify acupoints with similar characteristics.

2. Methods

2.1. Data extraction and processing

Data extraction was performed as described previously.¹¹ Briefly, acupoint data were extracted after searching the CDSR using the keyword “acupuncture.” To ensure an adequate number of studies for each disease, only review studies featuring more than three clinical trials were included. Studies using non-needle type acupuncture (e.g., acupressure) or acupuncture stimulating only a single part of the body (e.g., ears, face, head, or feet) were excluded. Based on these criteria, a total of 421 randomized controlled trials of 30 diseases were included.

Among the assembled acupoints, we calculated the frequency of each acupoint for each disease by dividing the number of counts for a given acupoint used for each disease by the sum of all acupoints used for the disease. The Acusynth database containing acupoint frequencies for 30 diseases was constructed in a prior study analyzing acupuncture indications (Fig. 1A).¹¹ Acusynth includes a 361×30 matrix for 361 acupoints and 30 diseases, with data available upon request.¹⁴ In the current study, the frequencies of five-phase acupoints were extracted from the Acusynth database and visualized using Orange Software (version 3.28.0, <https://orangedatamining.com>) (Fig. 1B). Analysis of variance (ANOVA) and

post-hoc Tukey’s tests were employed to analyze the differences among five-phase groups using Jamovi Software (version 0.9, <https://www.jamovi.org>). Furthermore, the same frequency dataset was used for nonmetric MDS and K-means clustering with R software (Fig. 1C) (version 4.0.3, <https://cran.r-project.org>).

2.2. MDS analysis of five-phase acupoints

MDS is a technique used to plot data as points based on their similarities or dissimilarities as represented by distance.¹³ As the frequency dataset consisted of each acupoint’s frequencies for 30 diseases, this multidimensional dataset is too complex for deriving the characteristics of each acupoint. MDS was therefore performed to reduce the dimensionality of the dataset and visualize the properties of each five-phase acupoint. Acupoints prescribed in a similar manner were highly correlated in the two-dimensional plot. Specifically, the dimensionality of the dataset was reduced using nonmetric MDS, in which the rank order of pairwise distances is calculated instead of the precise values.¹⁵ Nonmetric MDS was performed using the isoMDS function in the R package MASS.

The validity of the dimensional reduction and the results of nonmetric MDS was evaluated according to Kruskal’s stress value, which was calculated thus:

$$\text{Kruskal's stress} = \sqrt{\frac{\sum (d_{ij} - \hat{d}_{ij})^2}{\sum (d_{ij}^2)}}$$

where d_{ij} is the Euclidean distance between two points and \hat{d}_{ij} is the disparity due to the transformation to reduce dimensionality. There is a minimum number of dimensions needed to minimize stress and preserve the rank order of the original data.¹⁶ Stress values lower than 5% are considered good, those ≥ 5 and $< 10\%$ are considered fair, and those ≥ 10 and $< 20\%$ are considered poor.¹⁷

2.3. Cluster analysis of acupoint properties identified via MDS

To group the five-phase acupoints based on their similarities, K-means clustering was applied. K-means clustering is a widely used clustering algorithm that minimizes the sum of squared distances of each cluster’s data from the cluster center, thereby finding the lowest number of centroids K for a given dataset.¹⁸ Clustering was

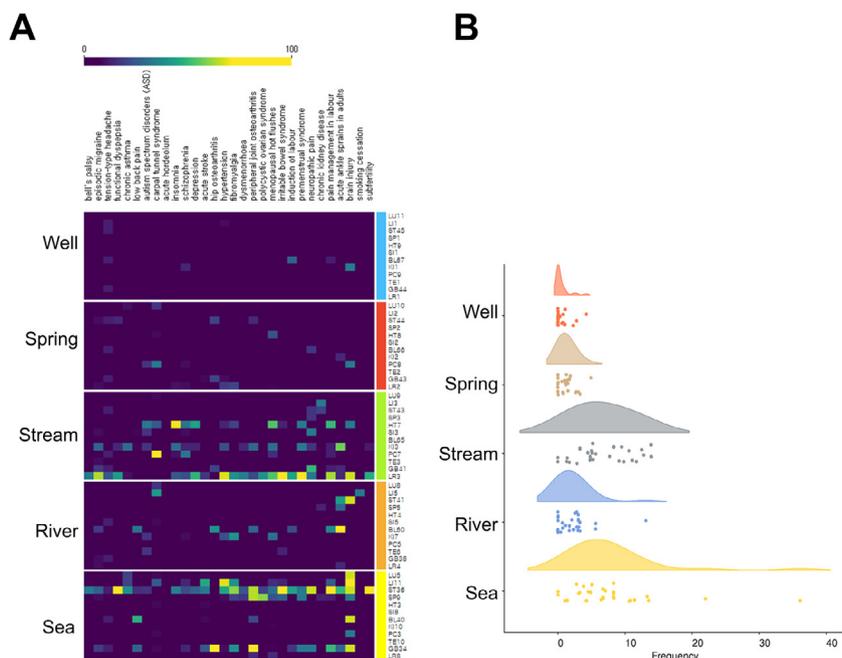


Fig. 2. Comparison of five-phase acupoint usage frequencies. (A) Usage frequencies of the five-phase acupoints were visualized in a heat map. (B) Higher frequencies were observed for stream and sea acupoints compared to well, spring, and river acupoints.

conducted on the results of MDS, with each vector in the plot representing an acupoint. In this study, K-means clustering was computed using the K-means function with Hartigan-Wong’s algorithm in the R package STATS. The maximum number of iterations was 10,000, and K was selected using the elbow method. Prior to clustering of the MDS vectors, we calculated the within-cluster sum of squares for each K ranging from 1 to 20. The elbow, the position at which a rapid decrease in the within-cluster sum of squares changes to a slower decrease, appeared initially at K = 4.¹⁹

3. Results

3.1. Use of five-phase acupoints in trials listed in the CDSR

The frequencies of five-phase acupoints are shown in Fig. 2A. The frequency of use of Five-phase acupoints was displayed in a 60 × 30 matrix table (60 acupoints and 30 diseases). The heat map revealed that stream and sea acupoints were both frequently used across the 30 diseases. The frequencies of the stream and sea acupoints were generally higher than those of the well, spring, and river acupoints (Fig. 2B). ANOVA revealed that the average frequency for the 30 diseases differed significantly among the five-phase acupoint groups ($F = 23.4, p < 0.05$). According to the post-hoc tests, the stream and sea acupoints were significantly more commonly used than the other acupoints (well: 0.47 ± 0.18 , spring: 1.27 ± 0.22 , stream: 6.60 ± 0.75 , river: 2.16 ± 0.48 , sea: 7.71 ± 1.29).

An illustration of the locations and frequencies of the five-phase acupoints of the gall bladder meridian is shown in Fig. 3, along with a depiction of the flow of Qi along the meridian.

3.2. MDS analysis of the five-phase acupoints

All five-phase acupoints were visualized in a two-dimensional plot based on similarities in their prescription patterns (Fig. 4A). To reduce the complexity of the data, we calculated the minimum number of dimensions needed to maintain the overall fit of the data. Two dimensions were shown to be sufficient and produced

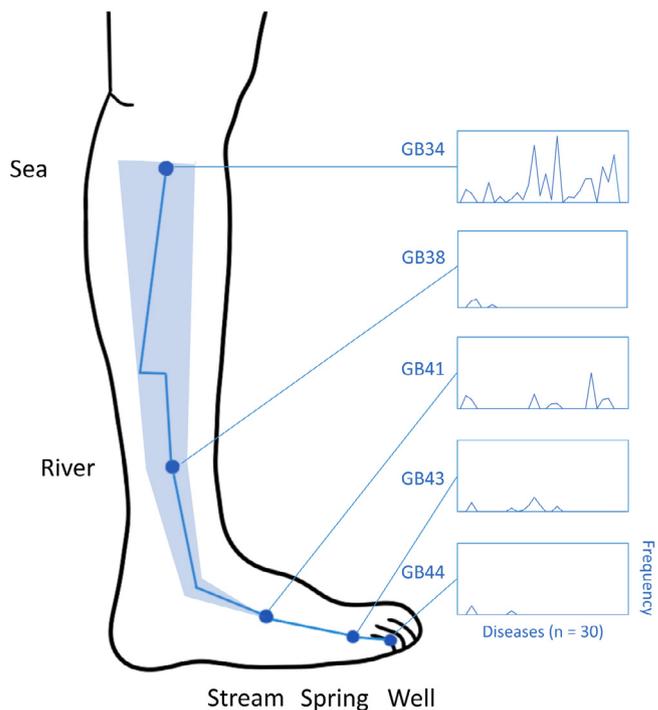


Fig. 3. The gall bladder meridian as an example of the five-phase acupoint pattern for 30 diseases. The flow of Qi (colored in blue) showing a wider Qi path as it moves towards the knee. The five-phase acupoint pattern presented on the right shows the usage frequencies of each acupoint (connected in lines) for the 30 diseases. The frequencies were higher and more widely distributed across the diseases for stream and sea acupoints compared to well, spring, and river acupoints.

a fair fit (Kruskal stress = 9.6%). After the number of dimensions were set, acupoints were mapped onto the two-dimensional MDS plot with their five-phase groups labeled in different colors. The well, spring, and river acupoints were closely related and hard to distinguish from one another. On the other hand, the stream and

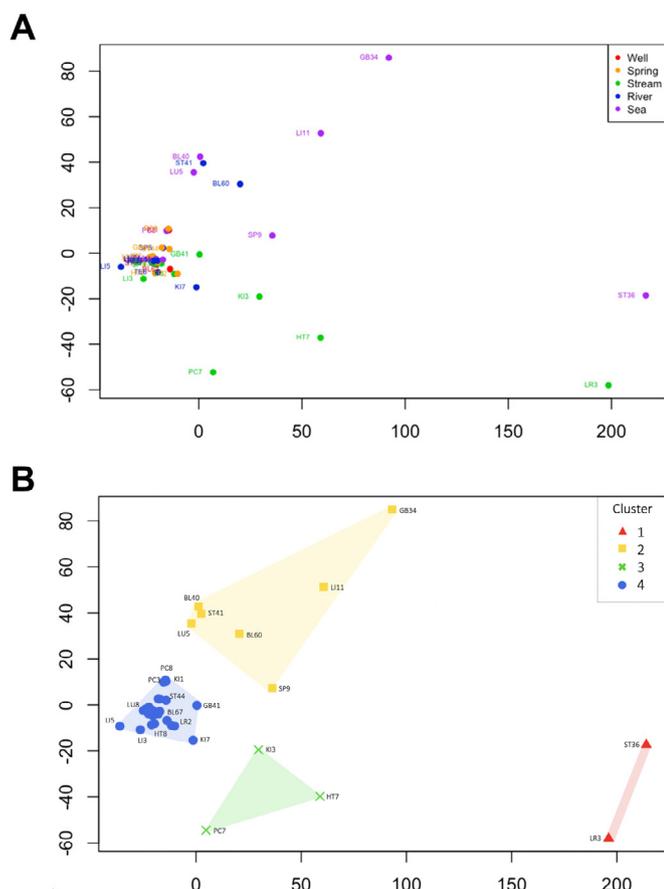


Fig. 4. Characteristics of the five-phase acupoints based on MDS and K-means clustering. (A) Five-phase acupoints are visualized using MDS. Each of the five-phase properties is labeled. Stream and sea acupoints formed a distinct cluster in the plot. (B) K-means clustering of the MDS results for the five-phase acupoints. The acupoints were clustered into four groups (cluster 1 marked with red triangles, cluster 2 marked with yellow squares, cluster 3 marked with green diagonal crosses, and cluster 4 marked with blue circles).

sea acupoints were relatively further apart, revealing their own unique properties in terms of acupuncture prescription.

3.3. Cluster analysis of five-phase acupoints based on MDS results

The MDS vectors were grouped into four clusters, which are presented in four different colors and shapes in Fig. 4B. The first cluster included the LR3 and ST36 acupoints, which are frequently used in most diseases. Cluster 2 consists of the LU5, BL40, ST41, BL60, SP9, LU11, and GB34 acupoints. The PC7, KI3, and HT7 acupoints were grouped in cluster 3, whereas all remaining acupoints were assigned to cluster 4.

4. Discussion

In the current study, we explored the use of five-phase acupoints in clinical trials and revealed characteristics of these acupoints using machine-learning methods. Among the five-phase acupoints, stream and sea acupoints were the most frequently used in the studies listed in the CDSR, whereas the well, spring, and river acupoints were relatively less commonly used. MDS and cluster analysis revealed that the LR3 (stream), ST36 (sea), GB34 (sea), BL60 (river), KI3 (stream), LI11 (sea), and HT7 (stream) acupoints exhibited their own characteristics based on distances representing the similarity between acupoint indications. These results suggest

that stream and sea acupoints are more likely to exhibit unique properties, compared to the other acupoints.

The five-phase acupoints were not used equally to treat diseases. Kim et al. demonstrated clear differences in the prescription of five-phase acupoints by analyzing the selection of these acupoints in classic medical textbooks.⁵ They found that spring, stream, and sea acupoints were more commonly used compared to well acupoints.⁵ In the current study, data mining also revealed that stream and sea acupoints were more frequently used in clinical trials compared to other acupoints. The stream acupoints for the meridians of five visceral organs (liver, heart, spleen, lung, and kidney) are equivalent to the source acupoints of those meridians and are therefore regarded as sites where innate Qi remains and reveals the conditions of the visceral organ (e.g., deficiency or excess of visceral Qi). On the other hand, the stream acupoints for the meridians of six bowel organs are not considered the source acupoints for those meridians and are therefore less important for treating internal organs. We found that stream acupoints corresponding to the liver, heart, and kidney meridians exhibited distinguishing characteristics, whereas none of the stream acupoints for the six bowel organs were highlighted by the MDS analysis, suggesting that the stream acupoints for the five visceral organs are more likely to have acupoint-specific treatment effects. Based on the traditional theory, sea acupoints of meridians have been widely used for the treatment of problems in six bowel organs. We found that the sea acupoints for the stomach (ST36), gall bladder (GB34), and large intestine (LI11) were located far from the other acupoints on the MDS plot. The results for the stream acupoints for the five visceral organ meridians and the sea acupoints for the six bowel organ meridians may be indicative of acupoint-specific effects. On the other hand, the use of well acupoints to treat diseases was extremely limited in the present study. Traditionally, well acupoints are primarily used to treat acute diseases,^{20, 21} with indications limited to the induction of labor and brain injury in the current database. Given that the clinical trials covered only a small number of acute diseases, we cannot rule out the possibility that the discrepancies in the usage rate of the five-phase acupoints may be related with the characteristics of the included diseases. Further studies examining a wider range of diseases will therefore be necessary to verify the different use patterns of the five-phase acupoints.

Clustering results in this study were as follows: the LR3 and ST36 acupoints were grouped in cluster 1; the LU5, BL40, ST41, BL60, SP9, LI11, and GB34 acupoints were grouped in cluster 2; the PC7, KI3, and HT7 acupoints were grouped in cluster 3; and other acupoints such as PC3, KI1, LU8, and LI3 were grouped in cluster 4. Of these locations, the LR3 (stream) and ST36 (sea) acupoints are representative of so-called major acupoints and have been widely used to treat many different conditions.²² The general effects of the major acupoints are explained by descending analgesia and central regulation,^{2, 23} and cluster 1 may represent acupoints that exhibit general efficacy for a wide variety of conditions. For cluster 2, the LU5 (sea), BL40 (sea), ST41 (river), BL60 (river), SP9 (sea), LI11 (sea), and GB34 (sea) acupoints are commonly used in diseases of the musculoskeletal system, nervous system, and injuries.²⁴⁻²⁷ Cluster 2 included four sea acupoints and two river acupoints, suggesting that these acupoints may be related to diseases of the six bowel organs or corresponding meridians. On the other hand, PC7, KI3, and HT7 are all source acupoints of visceral organs including the heart, pericardium, and kidney, and these acupoints may be associated with the regulation of emotional reactions and problems related to visceral organs.²⁸⁻³¹

Five-phase acupoints are defined as the five acupoints of the meridians located below the elbow and knee areas in the limb extremities.^{5, 7} Each of the five acupoints are allocated to one of five elements and manage the flow of Qi from the peripheral extrem-

ities to the trunk.^{5, 32} Among the various acupoints, practitioners select only a subset of acupoints that are relevant to the disease. It is therefore important to identify the most appropriate acupoints for the effective treatment of each disease. The current study revealed specific patterns of the five-phase acupoints from a clinical trial database. For instance, the GB41 (stream) and GB34 (sea) acupoints were more likely to be prescribed to treat various diseases within a given meridian (Fig. 3). As depicted in Fig. 3, starting from the well acupoint, Qi is initially superficial and dynamic as it flows towards the trunk, with the flow of Qi subsequently becoming wider and deeper. Therefore, superficial needling is sufficient to produce appropriate De-Qi sensations at well and spring acupoints, whereas deeper needling is needed for river and sea acupoints.³³ Although the origin of five-phase acupoints was derived from the concept of Qi flow, we argue that we should not strictly adhere to the original meaning of the five-phase acupoints. Data-driven approaches will improve our understanding of the five-phase acupoints and lead to the establishment of new models of analysis and educational resources for acupoint characteristics.

Our study still has several limitations. First, the diseases analyzed in this study cannot fully represent the use of acupuncture under real-world conditions. However, the 30 diseases selected represents a large spectrum of diseases affecting the nervous system (6 studies), genitourinary system (5), digestive system (2), musculoskeletal system (2), circulatory system (1), and respiratory system (1), as well as mental, behavioral, and neurodevelopmental disorders (4) and other disorders.¹¹ Further investigations examining a wider selection of diseases may reveal more clinically meaningful results. Second, this study presented the contents of the Acusynth database in an easily comprehensible plot, but more studies are needed to fully characterize the dimensions of the data. In this analysis, we identified which acupoints are clearly distinguishable from the other acupoints; however, we could not specify how and why those acupoints are located far from the other acupoints in the MDS plot. Further identification of factors that contribute to differences between acupoints will improve current approaches in the field of acupuncture studies.

In conclusion, this study characterized the five-phase acupoints used in randomized control trials by means of data mining and dimensional reduction. MDS and clustering suggested that stream and sea points are more likely to exhibit their own unique properties. Data-driven approaches such as this will improve our understanding of five-phase acupoints and facilitate the establishment of new models of analysis and educational resources for major acupoint characteristics.

CRedit author contributions statement

Seoyoung Lee: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Yeonhee Ryu:** Visualization. **Hi-Joon Park:** Conceptualization. **In-Seon Lee:** Formal analysis, Methodology, Writing – original draft. **Younbyoung Chae:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Funding

This research was supported by Korea Institute of Oriental Medicine (KSN1812181) and the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (No.2020R1A4A1018598).

Ethical statement

Not applicable.

Data availability

The authors can provide data upon reasonable request.

References

- MacPherson H, Maschino AC, Lewith G, Foster NE, Witt CM, Vickers AJ, et al. Characteristics of acupuncture treatment associated with outcome: an individual patient meta-analysis of 17,922 patients with chronic pain in randomised controlled trials. *PLoS ONE*. 2013;8(10):e77438.
- White A. Western medical acupuncture: a definition. *Acupunct Med*. 2009;27(1):33–35.
- Jung WM, Lee SH, Lee YS, Chae Y. Exploring spatial patterns of acupoint indications from clinical data: a STROBE-compliant article. *Medicine (Baltimore)*. 2017;96(17):e6768.
- Jung WM, Lee T, Lee IS, Kim S, Jang H, Kim SY, et al. Spatial patterns of the indications of acupoints using data mining in classic medical text: a possible visualization of the meridian system. *Evid Based Complement Alternat Med*. 2015;2015.
- Kim DH, Baik YS. A study on the clinical application of five-transport points in huangdineijing - focused on frequency of application and selection. *Kor J Acu*. 2020;37(4):276–283.
- Ahn CB, Jang KJ, Yoon HM, Kim CH, Min YK, Song CH, et al. A study of the Sa-ahm five element acupuncture theory. *J Acupunct Meridian Stud*. 2009;2(4):309–320.
- Kye K, Kim B. A theoretical study on acupuncture methods using five transport points. *J Kor Med*. 2021;42(1):59–74.
- Park IS, Jung WM, Lee YS, Hahm DH, Park HJ, Chae Y. Characterization of FiveShu acupoint pattern in Saam acupuncture using text mining. *Kor J Acu*. 2015;32(2):66–74.
- Chae Y, Ryu Y, Jung WM. An analysis of indications of meridians in DongUi-BoGam using data mining. *Kor J Acu*. 2019;36(4):292–299.
- Hwang YC, Lee IS, Ryu Y, Lee YS, Chae Y. Identification of acupoint indication from reverse inference: data mining of randomized controlled clinical trials. *J Clin Med*. 2020;9(9).
- Hwang YC, Lee IS, Ryu Y, Lee MS, Chae Y. Exploring traditional acupuncture point selection patterns for pain control: data mining of randomised controlled clinical trials. *Acupunct Med*. 2020.
- Lee IS, Chae Y. Identification of major traditional acupuncture points for pain control using network analysis. *Acupunct Med*. 2020.
- Borg I, Groenen PJF. *Modern Multidimensional scaling: Theory and Applications*. 2nd ed. Springer Science & Business Media; 2005.
- Choi DH, Lee S, Lee IS, Ryu Y, Chae Y. Characteristics of source acupoints: data mining of clinical trials database. *Kor J Acu*. 2021;38(2):100–109.
- Vardar Y, Wallraven C, Kuchenbecker K. 2019 *IEEE World Haptics Conference (WHC)*. Fingertip interaction metrics correlates with visual and haptic perception of real surfaces. IEEE; 2019.
- Kruskal JB. Nonmetric multidimensional scaling: a numerical methods. *Psychometrika*. 1964;29:115–129.
- Kruskal JB. Multidimensional scaling by optimizing goodness of fit to a non-metric hypothesis. *Psychometrika*. 1964;29:1–27.
- Mavroudis D, Marchiori E. Feature selection for k-means clustering stability: theoretical analysis and an algorithm. *Data Min Knowl Disc*. 2014;28:918–960.
- Galeati G, Rossi G, Pini G, Zilli G. Optimization of a snow network by multivariate statistical analysis. *Hydrological Sci J*. 1986;31(1):93–108.
- Li B, Zhou X, Yi TL, Xu ZW, Peng DW, Guo Y, et al. Bloodletting puncture at hand twelve jing-well points improves neurological recovery by ameliorating acute traumatic brain injury-induced coagulopathy in mice. *Front Neurosci*. 2020;14:403.
- Yu NN, Xu ZF, Gao Y, Zhou ZL, Zhao X, Zhou D, et al. Wake-promoting effect of bloodletting puncture at hand twelve JING-well points in acute stroke patients: a multi-center randomized controlled trial. *Chin J Integr Med*. 2020.
- Lee YS, Ryu Y, Yoon DE, Kim CH, Hong G, Hwang YC, et al. Commonality and specificity of acupuncture point selections. *Evid Based Complement Alternat Med*. 2020;2020.
- Chae Y, Chang DS, Lee SH, Jung WM, Lee IS, Jackson S, et al. Inserting needles into the body: a meta-analysis of brain activity associated with acupuncture needle stimulation. *J Pain*. 2013;14(3):215–222.
- Bae SJ, Lim J, Lee S, Choi H, Jang JH, Kim YK, et al. Augmented mechanical forces of the surface-modified nanoporous acupuncture needles elicit enhanced analgesic effects. *Front Neurosci*. 2019;13:652.
- Chae Y, Lee H, Kim H, Kim CH, Chang DI, Kim KM, et al. Parsing brain activity associated with acupuncture treatment in Parkinson's diseases. *Mov Disord*. 2009;24(12):1794–1802.
- Kim NH, Cho SY, Jahng GH, Ryu CW, Park SU, Ko CN, et al. Differential localization of pain-related and pain-unrelated neural responses for acupuncture at BL60 Using BOLD fMRI. *Evid Based Complement Alternat Med*. 2013;2013.
- Lee IS, Lee SH, Kim SY, Lee H, Park HJ, Chae Y. Visualization of the Meridian system based on biomedical information about acupuncture treatment. *Evid Based Complement Alternat Med*. 2013;2013.

28. Chae Y, Park HJ, Kang OS, Lee HJ, Kim SY, Yin CS, et al. Acupuncture attenuates autonomic responses to smoking-related visual cues. *Complement Ther Med.* 2011;19(Suppl 1):S1–S7.
29. Li CR, Cheng ZD, Zhang ZX, Kim A, Ha JM, Song YY, et al. Effects of acupuncture at Taixi acupoint (KI3) on kidney proteome. *Am J Chin Med.* 2011;39(4):687–692.
30. Park HJ, Chae Y, Jang J, Shim I, Lee H, Lim S. The effect of acupuncture on anxiety and neuropeptide Y expression in the basolateral amygdala of maternally separated rats. *Neurosci Lett.* 2005;377(3):179–184.
31. Zhu B, Wang Y, Zhang G, Ouyang H, Zhang J, Zheng Y, et al. Acupuncture at KI3 in healthy volunteers induces specific cortical functional activity: an fMRI study. *BMC Complement Altern Med.* 2015;15:361.
32. Sun BG, Meng J, Xiang T, Chen ZX, Zhang SJ. Acupuncture of the Five Shu Acupoints in spleen meridian to lower blood uric acid level. *Ann Palliat Med.* 2014;3(1):22–27.
33. Yin C, Park JB, Lee JY, Chae Y, Jang WC, Kim ST, et al. Acupuncture perception (Deqi) varies over different points and by gender with two distinct distribution patterns of dullness and pain. *J Sens Stud.* 2009;24(5):635–647.