Analysis of prescription medication rules of traditional Chinese medicine for bradyarrhythmia treatment based on data mining

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Abstract

Background: Multiple studies have revealed that Traditional Chinese Medicine (TCM) prescriptions can provide protective effect on the cardiovascular system, increase the heart rate and relieve the symptoms of patients with bradyarrhythmia. In China, the TCM treatment of bradyarrhythmia is very common, which is also an effective complementary therapy. In order to further understand the application of Chinese medicines in bradyarrhythmia, we analyzed the medication rules of TCM prescriptions for bradyarrhythmia by data mining methods based on previous clinical studies.

Methods: We searched studies reporting the clinical effect of TCM on bradyarrhythmia in the PubMed and Chinese databases China National Knowledge Infrastructure database, and estimated publication bias by risk of bias tools ROB 2. Descriptive analysis, hierarchical clustering analysis and association rule analysis based on Apriori algorithm were carried out by Microsoft Excel, SPSS Modeler, SPSS Statistics and Rstudio, respectively. Association rules, co-occurrence and clustering among Chinese medicines were found.

Results: A total of 48 studies were included in our study. Among the total 99 kinds of Chinese medicines, 22 high-frequency herbs were included. Four new prescriptions were obtained by hierarchical cluster analysis. 81 association rules were found based on association rule analysis, and a core prescription was intuitively based on the grouping matrix of the top 15 association rules (based on confidence level), of which Guizhi, Zhigancao, Wuweizi, Chuanxiong, Danshen, Dongguai, Huangqi, Maidong, Danshen, Rougui were the most strongly correlated herbs and in the core position.

Conclusion: In this study, data mining strategy was applied to explore the TCM prescription for the treatment of bradyarrhythmia, and high-frequency herbs and core prescription were found. The core prescription was in line with the treatment ideas of TCM for bradyarrhythmia, which could intervene the disease from different aspects and adjust the patient’s Qi, blood, Yin and Yang, so as to achieve the purpose of treatment.

Abbreviation: TCM = traditional Chinese medicine.

Keywords: bradyarrhythmia, bradycardia, Chinese medicine, data mining, prescription medication rules

1. Introduction

Bradyarrhythmia is a common clinical arrhythmia. It is usually attributed to physiological conditions (e.g., well trained athletes), drug toxicity, genetic mutations, concurrent issues, or advanced age.\textsuperscript{[1,2]} Pathological changes that cause bradyarrhythmia are usually located in the sinus node, atrioventricular nodal tissue, atrial tissue, and the specialized conduction system.\textsuperscript{[3]} It can be further classified as sinus node dysfunction or sick sinus syndrome, atrioventricular block, and conduction tissue disease, depending on the location of the disease.\textsuperscript{[4]} Severe symptomatic bradyarrhythmia can lead to syncpe and symptoms of heart failure, which can even be life-threatening.

The incidence of bradyarrhythmias is high in the elderly population, and a large cohort study has found that the incidence of bradyarrhythmias increases with age regardless of gender.\textsuperscript{[5]}

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The datasets generated during and/or analyzed during the current study are publicly available.

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With the acceleration of the aging process of the global population, the aging population base will continue to grow, and the number of patients with bradyarrhythmias will continue to increase. Therefore, bradyarrhythmia has received more attention around the world. The United States, Europe, China and other places are continuously updating their clinical guidelines or expert consensus for bradyarrhythmia, bringing new methods and strategies for the treatment of bradyarrhythmia.

Clinical treatment of bradyarrhythmia mainly includes two types: drug therapy and pacing therapy. Pharmacotherapy is indicated for acute management due to drug toxicity, while pacemaker implantation is the essential therapy for the treatment of irreversible symptomatic bradyarrhythmias. In recent years, the use of pacemaker implantation has continued to grow worldwide. However, postoperative complications such as infection and heart failure, high cost and lifelong follow-up need are also the reasons why many people refuse or cannot afford pacemaker implantation. Such populations are at greater risk for severe complications and other accidents, and there is an urgent need to find alternatives for them.

Traditional Chinese medicine (TCM) has a long history of treating bradyarrhythmias, which began in the Han dynasty in China (more than 2000 years ago). TCM has unique treatment advantages. It can be based on the development characteristics of the disease and from the concept of holism, to carry out syndrome differentiation and treatment, so as to adjust the Qi, blood, Yin and Yang inside and outside the human body, and achieve the therapeutic effect. For the pathogenesis of bradyarrhythmia, TCM theory is mostly considered to be due to blood stasis after Qi, Yang and Yin deficiency. Such populations are derived from screening the reference lists of included randomized controlled trials and previous meta-analysis studies. We aimed to comprehensively investigate the high-level clinical studies of Chinese medicine in the treating of bradyarrhythmias, so only randomized controlled trials in which TCM treatment shows exact therapeutic effect were included. In addition, included studies need to meet clinical diagnostic criteria for bradyarrhythmias. For the intervention methods, we hope to obtain all forms of herbal treatment: “bradyarrhythmia,” “bradycardia,” “sick sinus syndrome,” “sinus node dysfunction,” “atrioventricular block,” “traditional Chinese medicine,” “Chinese medicine,” “herbal medicine,” “randomized controlled trial,” and “clinical trial.” Additional studies were derived from screening the reference lists of included randomized controlled trials and previous meta-analysis studies.

3. Material and Method

3.1. Clinical data sources and selection criteria

Systematically searched Pubmed (Medline) and Chinese databases China National Knowledge Internet database to identify randomized studies of TCM for bradyarrhythmia published from January 2000 to January 2022, with no language restriction. The full search strategy was employed combinations of medical subject headings terms and text words around “bradyarrhythmia,” “bradycardia,” “sick sinus syndrome," “sinus node dysfunction,” “atrioventricular block,” “traditional Chinese medicine,” “Chinese medicine,” “herbal medicine,” “randomized controlled trial,” and “clinical trial.” Additional studies were derived from screening the reference lists of included randomized controlled trials and previous meta-analysis studies.

3.1.1. Inclusion criteria. We aimed to comprehensively investigate the high-level clinical studies of Chinese medicine in the treating of bradyarrhythmias, so only randomized controlled trials in which TCM treatment shows exact therapeutic effect were included. In addition, included studies need to meet clinical diagnostic criteria for bradyarrhythmias. For the intervention methods, we hope to obtain all forms of herbal treatment: China’s National Medical Products Administration (NMPA)-approved patent Chinese medicine, classical formulas, self-designed formulas, single herb, and TCM-derived products.

Special note: For the same prescription appearing in different studies, we only included it once.

3.1.2. Exclusion criteria. Non-clinical studies: reviews and animal experiments. Non-randomized studies: retrospective studies, prospective studies, cohort studies, case-control studies, observational clinical trials or case reports. Non-oral decoction...
therapies: acupuncture, massage, moxibustion, external Chinese medicine, cupping, ear-point embedding beans, physical therapies, etc.

3.2. Quality assessment

For the included studies, the Revised Cochrane risk-of-bias tool for randomized trials[30] was used to assess the risk of bias, including bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. In this way, all articles selected for inclusion in the study were graded under the categories of low, some concerns, or high risk of bias.

3.3. Data mining

3.3.1. Standardization of data. In this study, all translations (Chinese-English) were mainly in accordance with the “WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region”[31] and “International Standard Chinese-English Basic Nomenclature of Chinese Medicine.”[32] Chinese medicines were standardized with reference to the Chinese Pharmacopoeia 2020 edition[33] and unified as the official name.

3.3.2. Data analysis. All data were converted into transactional data, and the frequency of occurrence of each herb was subsequently calculated by an Excel pivot table,[34] into transactional data, and the frequency of occurrence of each item on the right hand side (RHS) and Y represents the consent level is the con-...
into the overall scatter diagram of all rules, with X axis as the support degree, Y axis as the confidence level, and the color of each association rule is determined by its lift value (Fig. 5). In this study, we found out the high-frequency of occurrence items in prescriptions based on mining association rules among herbs and filtered the top 15 rules based on the confidence level (Table 3).

With respect to grouped sets of items, we used association network graph based on color or size visualization to achieve the visualization of herbs compatibility relations (Fig. 6). These features are presented intuitively based on a grouping matrix of 15 association rules. This figure provides a clear representation of association rules and avoids cluttered presentation. It could be seen that Guizhi, Zhigancao, Wuweizi, Chuanxiong, Danshen, Danggui, Huangqi, Maidong, Dangshen, Rougui were the most strongly correlated herbs and in the core position.

5. Discussion

In recent years, with Professor Tu Youyou becoming the first Nobel Prize winner in Physiology or Medicine in China, TCM has attracted more and more attention from the international community.[84] In March 2022, a meeting report[85] released by the World Health Organization (WHO) also indicated that TCM was both safe and beneficial when combined with conventional antiviral medicine for coronavirus disease 2019.[86,87] Traditional, complementary, and integrative medicine can make important contributions to health management, disease prevention, and treatment of major diseases. Like artemisinin, extracted from Chinese herb Qinghao (Artemisiae Annuae Herba), Chinese medicines and its derivatives are generally inexpensive, while having a good therapeutic effect. Therefore, TCM treatment of bradyarrhythmia requires in-depth mining and analysis, which can benefit patients with bradyarrhythmia and allow such population to have more treatment options.

The nature and function of Chinese medicine formed the fundamental basis for analyzing Chinese herbs as well as its clinical applications. In this study, a variety of statistical methods were used to perform a holistic analysis of Chinese medicines in prescriptions for the treatment of bradyarrhythmia. Through descriptive statistical analysis of TCM data in prescriptions for the treatment of bradyarrhythmia, we found high-frequency Chinese medicines in TCM prescriptions, of which Danshen, Danggui, Chuanxiong, Honghua, and Taoren were commonly used in clinical practice for activating blood and resolving stasis, Huangqi, Zhigancao, Renshen, Dangshen, and Taizishen were commonly used in clinical practice for tonifying Qi, Fuzi, Guizhi, Hongshen, Yinyanghuo, Rougui, Xixin, and Mahuang were commonly used in clinical practice for warming Yang, Maidong, Wuweizi, Dihuang, Shanzhuyu were commonly used in clinical practice for nourishing Yin, and Gansong is a herb for moving Qi.

The application of hierarchical cluster analysis allowed us to find four potential TCM prescriptions for the treatment of...
| Study (year) | Study design | Inclusion criteria | Formula name | Herbs |
|-------------|--------------|-------------------|--------------|-------|
| Sun et al., 2020[36] | RCT | Bradyarrhythmia | Ginseng deer restorative decoction | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Ma et al., 2020[37] | RCT | Bradyarrhythmia | Fuxin capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Zou, 2020[38] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Cao et al., 2019[39] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Fang et al., 2019[40] | RCT | Bradyarrhythmia | Shenglv decoction | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Zhu, 2019[41] | RCT | Bradyarrhythmia | Shenglv decoction | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Xu et al., 2019[42] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Shao et al., 2019[43] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Fan et al., 2018[44] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Sun et al., 2018[45] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Xu et al., 2018[46] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Wei et al., 2018[47] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Zhang et al., 2018[48] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Zhang et al., 2017[49] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Ge et al., 2017[50] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Li et al., 2017[51] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Li et al., 2017[52] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Liu, 2015[53] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Lin et al., 2015[54] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Liu et al., 2014[55] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Bai et al., 2014[56] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Wu et al., 2014[57] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Zhou et al., 2014[58] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Liu et al., 2018[59] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Liu et al., 2018[60] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Liu et al., 2017[61] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Peng et al., 2012[62] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Ren et al., 2012[63] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Bai et al., 2011[64] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Zhang et al., 2011[65] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Guo, 2011[66] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Li et al., 2011[67] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Ma et al., 2010[68] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Li, 2008[69] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Wang et al., 2008[70] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Wang et al., 2007[71] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |
| Deng, 2006[72] | RCT | Bradyarrhythmia | Fumai capsule | Fu, Rougui, Sangi, Huanglian, Sangi, Mudanpi, Danshen, Gansong, Zhigancao |

(Continued)
Table 2

| No. | Chinese name  | Latin name* | Medicinal part | Frequency |
|-----|---------------|-------------|----------------|-----------|
| 1   | Danshen      | Salviae Miltiorrhizae Radix et Rhizoma | Root, Rhizome | 25        |
| 2   | Huangqi      | Astragali Radix | Root          | 24        |
| 3   | Fuzi         | Aconiti Lateralis Radix Praeparata | Root          | 23        |
| 4   | Zhigancao    | Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle | Rhizome   | 23        |
| 5   | Guizhi       | Cinnamomi Ramulus | Branch      | 21        |
| 6   | Maidong      | Ophiopogonis Radix | Root         | 16        |
| 7   | Danggui      | Angelicae Sinensis Radix | Root        | 13        |
| 8   | Renshen      | Ginseng Radix et Rhizoma | Root, Rhizome | 12        |
| 9   | Wuweizi      | Schisandrae Chinensis Fructus | Fruit       | 12        |
| 10  | Dangshen     | Codonopsis Radix | Root         | 11        |
| 11  | Hongshen     | Ginseng Radix et Rhizoma Rubra | Root, Rhizome | 11        |
| 12  | Yinyanghuo   | Epimedi Follum | Leaf         | 11        |
| 13  | Chuanxiong   | Chuanxiong Rhizoma | Rhizome | 8         |
| 14  | Rougui       | Cinnamomi Cortex | Bark        | 8         |
| 15  | Xixin        | Asari Radix et Rhizoma | Root, Rhizome | 8         |
| 16  | Dihuang      | Rehmanniae Radix | Root         | 7         |
| 17  | Mahuang      | Ephedrae Herba | Stem         | 7         |
| 18  | Shanzhuyu    | Corni Fructus | Fruit        | 7         |
| 19  | Gansong      | Nardostachyos Radix et Rhizoma | Root, Rhizome | 5         |
| 20  | Honghua      | Carthami Flos | Flower       | 5         |
| 21  | Taizhishen   | Pseudostellariae Radix | Root        | 5         |
| 22  | Taoren       | Persicae Semen | Seed        | 5         |

*The Latin names standardized by Chinese Pharmacopoeia (2020 edition).
Figure 3. High-frequency herbs co-occurrence diagram.

Figure 4. Hierarchical cluster analysis of high-frequency herbs.
bradyarrhythmia among high-frequency herbs. From Figure 4, it can be seen that the number of herbs in the first three prescriptions was more appropriate, while the fourth prescription only includes two herbs, Shanzhuyu and Gansong. Due to the small number of herbs, we did not consider it as a complete prescription. However, according to long-term clinical experience of TCM, we found that if the herb of prescription 4 and the herb of prescription 1 were combined into one prescription (prescription 5), the drug composition of this prescription was very close to the Chinese patent medicine “Shensong yangxin capsule (SSYX),” which has the functions of replenishing Qi and nourishing Yin, and activating blood and resolving stasis. Long-term SSYX treatment has been shown to restore calcium homeostasis and increase heart rate in the rabbit model of bradyarrhythmia by enhancing the expression of ryanodine receptor 2, sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\)ATPase 2 and voltage-dependent anion-selective channel.\(^{[88,89]}\) From the analysis of the medicinal efficacy of each herb in prescription 2, its clinical effect was similar to that of the classical prescription “Zhigancao decoction” in Treatise on Cold Pathogenic and Miscellaneous Disease,\(^{[90]}\) which has the effects of nourishing Yin and blood, warming Yang and replenishing Qi. The efficacy of prescription 3 is close to that of the classical prescription “Mahuangfuzixixin Decoction” and the Chinese patent medicine “Shenxian Shengmai oral liquid (SXSM),” which has the effect of warming Yang and activating blood. Studies have shown that SXSM can affect in calcium handling and signaling, promote myocardial oxidative phosphorylation and tricarboxylic acid cycle, improve adenosine triphosphate production, and stimulate sympathetic transmission by upregulating β1-adrenoreceptor, increasing acetylcholinesterase and reducing nicotinic receptors, thus increasing heart rate.\(^{[91,92]}\)

Through association rule analysis based on Apriori algorithm, we found 81 rules, which can show the correlation of herb compatibility. Based on the definition of confidence level, we believe that the compatibility of herbal medicines with low confidence has low reference value for clinical practice, only the first 15 association rules are selected, so as to summarize the core prescription of Chinese medicines for the treatment of bradyarrhythmia. According to the theory of TCM, the core prescription has the effects of warming Yang and activating blood, replenishing Qi and nourishing Yin, which may be potentially useful in the treatment of bradyarrhythmia. Further clinical and pharmacodynamic experiments are required to validate the observation results of this study and explore the main components and mechanism of action of the core prescription.

### 6. Conclusions

The data mining strategy was applied in this study to explore Chinese medicine prescriptions for the treatment of bradyarrhythmia, high-frequency herbs were selected, and then three potential prescriptions were found by hierarchical cluster analysis, and one core prescription was excavated by association rule analysis. The compatibility of herbal medicines in the above four prescriptions is consistent with the therapeutic strategy of TCM for bradyarrhythmia, which can intervene the disease from different aspects and adjust the Qi, blood, Yin and Yang of patients, so as to achieve the purpose of treatment. Data mining can combine a variety of statistical methods to analyze TCM clinical research data and discover more therapeutic strategies from different perspectives. However, such analysis is limited to the secondary analysis of existing literature data, and could not be deeply explored in terms of drug efficacy and mechanism of action. Therefore, the research results still need to be verified by clinical and pharmacodynamic studies.

### Author contributions

**Conceptualization**: Xujie Wang, Wantong Zhang, Weiliang Weng, Qiuyan Li.

**Data curation**: Xujie Wang, Xuexue Zhang, Biaoayan Hu.

**Formal analysis**: Xujie Wang, Biaoayan Hu.

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**Supervision**: Weiliang Weng, Qiuyan Li.

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Writing – review & editing: Jiwei Zhang, Wantong Zhang, Weiliang Weng, Quyan Li.

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