





CLINICAL ARTICLE

Current Treatment Modalities for Osteonecrosis of Femoral Head in Mainland China: A Cross-Sectional Study

Ze-qing Huang, MM^{1†} , Fan-yu Fu, BM^{2†} , Wen-long Li, MM³ , Biao Tan, MM¹ , Hai-jun He, MM¹ ,
Wen-gang Liu, MM⁴ , Wei-heng Chen, PhD³ 

¹Wangjing Hospital, China Academy of Chinese Medical Sciences and ³The Third Affiliated Hospital of Beijing University of Chinese Medicine, Beijing, ²Guizhou University of Traditional Chinese Medicine, Guiyang and ⁴The Second Hospital of Traditional Chinese Medicine of Guangdong Province, Guangdong, China

Objective: To investigate the application of treatment modalities for patients with osteonecrosis of the femoral head (ONFH) in mainland China.

Methods: This cross-sectional study was based on the online application of China Osteonecrosis of the Femoral Head Database (CONFHD). Between July 2016 to December 2018, the CONFHD program planned to recruit ONFH patients from 12 administrative areas across mainland China. Real-world medical records of treatment regimens for these patients, including surgeries and prescriptions, were approved to upload to the CONFHD application for further analysis. The surgeries performed on these patients were classified into total hip arthroplasty and hip-preserving procedures, and the latter was further classified into core decompression, bone grafting, and tantalum rod implantation. Prescription medications were classified into chemical medicine and Chinese herbal medicine (CHM); chemical medicine was further classified according to their chemical compounds, and CHM was classified according to therapeutic functions based on traditional Chinese medicine theory. Descriptive analysis was performed to summarize the application of different treatment regimens on the overall sample.

Results: A total of 1491 patients (2381 hips) who fulfilled the protocol criteria were included. There were 1039 males and 452 females with a mean age of 47.29 ± 12.69 years. The causes of ONFH were alcoholism in 642 patients (43%), corticosteroid in 439 patients (29%), trauma in 239 patients (16%), and idiopathic ONFH in 171 patients (11%). Operative treatments (including total hip arthroplasty and hip-preserving procedures) were performed on 49% of patients (43% of hips), chemical medicine therapy (including bisphosphonate, statins, and prostacyclin) was given to 37% of patients (37% of hips), and CHM was administrated to 72% of patients (75% of hips). The aforementioned interventions were not always used alone, since 47% of patients (52% of hips) received combined regimens with multiple interventions. Among hips treated by surgery, all hips with ARCO stage IV ONFH received THA (305 hips), and THA was also performed on 63 hips with stage II ONFH. Over half of hips with stage I (81%), II (91%), and III (92%) ONFH had received pharmacological treatments. Prostacyclin and bisphosphonate were the top two most prescribed medicines used alone. CHM therapies with multiple CHM functions were more commonly prescribed.

Address for correspondence Wei-heng Chen PhD, The Third Affiliated Hospital of Beijing University of Chinese Medicine, No. 51 Anwai Xiaoguanjie, Chaoyang District, Beijing, China 100029 Tel: 86 10 84980281; Fax: 86 10 84981092; Email: drchenweiheng@bucm.edu.cn

[†]These authors contributed equally to this work.

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Conclusion: Current treatment modalities for ONFH patients in mainland China include operative treatment, chemical medicine, and CHM. Combined regimens with different treatment modalities are common in real-world clinical practices.

Key words: Clinical guideline; Cross-sectional study; Osteonecrosis of the femoral head; Pharmacological treatment; Surgery

Introduction

Osteonecrosis of the femoral head (ONFH) is the final common pathway of a complex interplay of genetic anomalies and stimulus factors that results in the loss of blood supply to the femoral head of the femur¹. Although the detailed mechanism remains unknown, the most common stimulus factors include long-term corticosteroid therapy, alcohol abuse, and hip injury. Disruption of blood supply to the femoral head would lead to the ischemia of subchondral osseous tissue, which further reduces its support strength and self-repair function. If left untreated, ONFH would rapidly progress to the femoral head collapsing and the destruction of the hip joint². Most patients with femoral head collapse could experience progressive symptoms, including groin pain and restricted physical function; hence they might live dependent lives and have to leave their workplace. Those collapse patients who have developed severe hip osteoarthritis might have to undergo total hip arthroplasty (THA) to restore their physical functions. Since ONFH primarily affects the young or middle-aged population, it is among the most important causes of disability and THA in this population³.

However, THA is not the first choice for ONFH since the implant lifespan and revision surgery are still tricky problems⁴. On the other hand, some patients themselves with severely restricted physical functions are unwilling to choose the THA option. Apart from THA, various other treatments have been suggested for ONFH, which can be categorized into hip-preserving procedures and pharmacological treatments⁵. These treatments would help improve clinical outcomes when given to those patients with pre-collapse ONFH, but they are also applied to patients with femoral head collapse in the real world. The most frequently used hip-preserving procedures include core decompression, bone grafting, rotational osteotomy, and tantalum rod implantation^{6, 7}. A few chemical medicines are currently used to treat ONFH as well, including bisphosphonates, statins, low molecular weight heparin, and prostacyclin⁸. Additionally, the situation is a bit different in China. Chinese herbal medicine (CHM), usually oral decoctions that consist of several Chinese herbs⁹, is commonly prescribed for patients with ONFH.

China may be one of the countries that own the most patients with ONFH, and it is estimated that there are over 8 mn ONFH patients on the China mainland¹⁰. The proper management of this large patient population is a challenging problem. To solve this problem, Chinese experts had developed several versions of consensus or guidelines for the diagnosis and

treatments of ONFH during the past decade¹¹⁻¹⁴. However, the implementation of the therapeutic guidelines could be problematic. Clinical practitioners who are responsible for the medical management of these patients, may not adhere to the agreed guidelines due to various reasons. Therefore, the status quo of how these medical interventions are used is still unclear.

Real-world application of the recommended treatments is rather a different but complicated problem. It is of importance to investigate the implementation of the recommended treatments, to further optimize the management of ONFH patients and update the clinical guidelines. Hence, the main objective of this work is to address the following issues: (i) What treatment modalities are currently performed for ONFH patients in mainland China? (ii) What are the stage indications of each treatment modality in real-world clinical practice? (iii) How are the treatment modalities used in real-world clinical practice, as a single treatment regimen or a combined regimen?

Materials and Methods

Study Design

This cross-section investigation was based on nationwide data from the China Osteonecrosis of Femoral Head Database (CONFHD, <http://onfh.keyanyun.com/>) program. The CONFHD program was established in 2015 with the purpose of improving medical management of ONFH patients in mainland China. Between 2016 and 2018, the CONFHD program planned to recruit 2400 ONFH patients (200 patients for each sampling area) by joint efforts of 25 public hospitals from 12 administrative areas (provinces or municipalities) across mainland China. The sampling areas included Beijing municipality, Shanghai municipality, Shandong province, Henan province, Guangxi province, Shan'xi province, Guangdong province, Jiangsu province, Fujian province, Hubei province, and Jilin province.

The diagnosis of ONFH was performed based on positive features seen on magnetic resonance imaging (MRI), including a focal serpentine low-signal band with fatty center on T1 weighted image, and serpiginous peripheral dark line and bright inner line on T2 weighted image (double line sign)^{11, 13, 14}. Inclusion criteria were: (i) newly diagnosed cases within 3 months; (ii) an age of over 18 years; (iii) a consecutive medical record with a follow-up duration of more than 3 months on the CONFHD application. Exclusion criteria were: (i) a history of any treatment for ONFH;

(ii) pregnancy or lactation; and (iii) undergoing other medical treatments for primary diseases.

Data Collection

The CONFHD program provides an online platform for follow-up of the study patients. Real-time treatment regimens, including medical records, surgeries, and prescriptions for each patient, were uploaded to the database by research secretaries. The research secretaries were not involved in the medical management of ONFH patients. The attending doctors were not involved in the present study as well, so the treatment regimen of each patient was made by the consultation of doctors and patients themselves. As of 2019, anonymous treatment regimen records of the patient participants were exported and analyzed.

Operative Treatments

The operative treatments used were categorized according to the Chinese guidelines^{11, 13, 14}, including core decompression, bone grafting, tantalum rod implantation, and THA. Core decompression is limited to percutaneous procedures aiming to drill a tunnel into the necrotic lesion without injections of adjunct biologic agents. Bone grafting

procedures refer to open or percutaneous operation to debride the necrotic lesion and replace it with vascularized bone or non-vascularized bone. Tantalum rod implantation refers to the implantation of tantalum rod into the femoral head to increase its supporting capacity. THA is limited to procedures where the femoral head and acetabulum are removed and replaced with prosthetic components.

Pharmacological Treatments

The chemical medicines used were easily categorized by their chemical compounds, including bisphosphonate, statins, low molecular weight heparin (LMWH), and prostacyclin. Bisphosphonates refer to a class of drug that reduces osteoclast activity, which are limited to alendronate and zoledronic acid in the present study. Statins included in the present study are atorvastatin and pravastatin. LMWH is limited to nadroparin, enoxaparin, and dalteparin. Prostacyclin includes beraprost and alprostadiol.

CHM, however, is not easy to categorize by the constituent herbs since it is a combination of usually more than 10 kinds of different herbs, but it can be categorized according to the CHM functions. The CHM function refers to the clinical effect of CHM based on the theory of

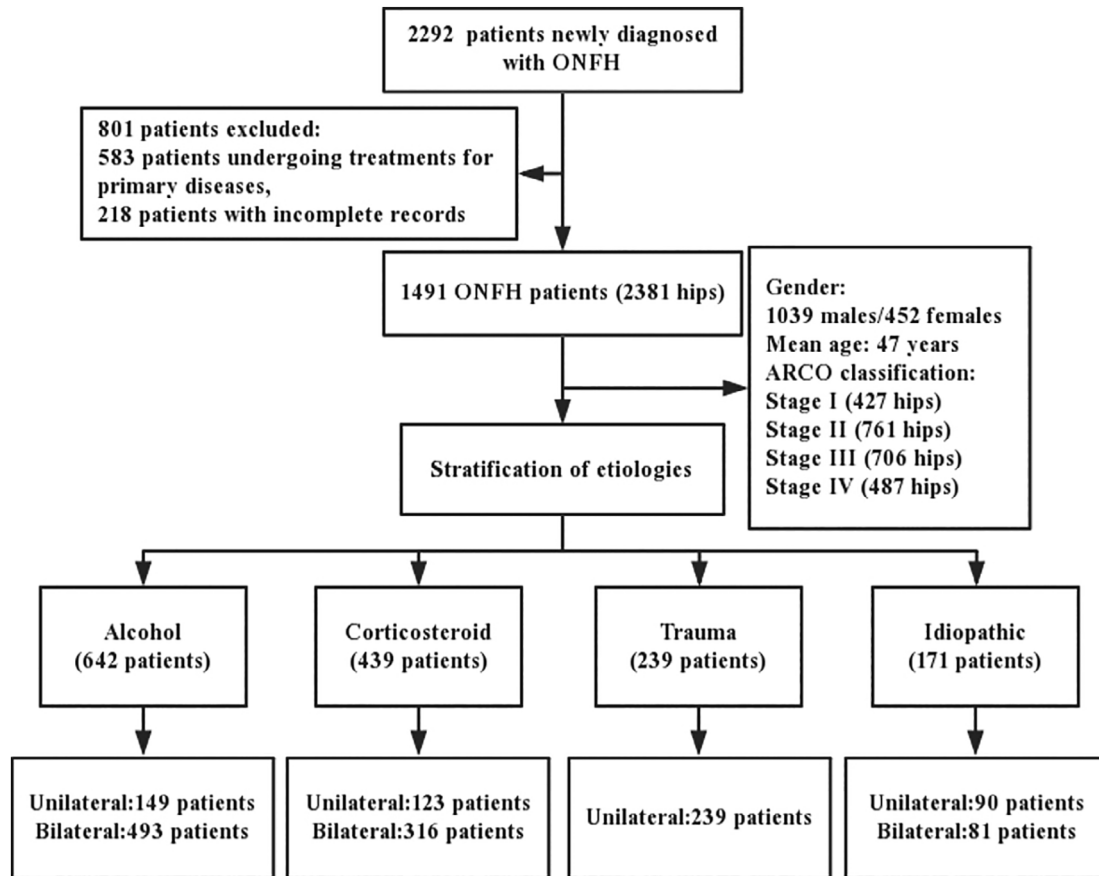


Fig. 1 Flow diagram detailing the recruitment and baseline characteristics of the 1491 ONFH patients. ONFH = Osteonecrosis of the femoral head. ARCO = Association Research Circulation Osseous.

Traditional Chinese Medicine (TCM). Chinese guidelines had recommended the use of Chinese herbs with special CHM functions, including clearing dampness (Qu-Shi), resolving phlegm (Hua-Tan), and activating blood circulation (Huo-Xue)¹¹⁻¹⁴. Since a CHM prescription may contain different herbs with different CHM functions, we also made the following rule for better analysis. In every single prescription of CHM, if the number of herbs with the same CHM function exceeded 1/4 of the total number of herbs, then the CHM function of these herbs was the function of this prescription. A pharmacist who majored in the science of Chinese materia medica was invited to categorize the CHM function of the CHM prescriptions. The pharmacist was not involved in the present study.

Assessments of Treatment Regimens

The treatment regimens were classified into single regimens and combined regimens. A single regimen referred to when only one kind of treatment modality was used for a patient, such as using operative treatment alone. A combined regimen referred to when more than two kinds of treatment modalities were used for a patient, such as combining operative

treatment with chemical medicine. Since ONFH is a tricky disease that necessitates long-term observation, only those pharmacological treatments that had been continuously used for at least 3 months were taken into analysis.

Statistical Analysis

Descriptive analysis was performed to describe the application status of different treatment regimens on the overall sample. Means were given with standard deviation for continuous variables and percentages with 95% CIs were given for categorical variables.

Results

From July 2016 to December 2018, the CONFHD program had registered 2292 patients who were newly diagnosed with ONFH in our cooperative hospitals, but only 1491 patients (2381 hips) who fulfilled our criteria were included in the present study. Among these 1491 patients, there were 1039 males and 452 females with a mean age of 47.29 ± 12.69 years (range, 18 to 72 years). Of the 1491 patients, 890 had bilateral ONFH, and 601 had unilateral ONFH. The causes of ONFH were alcoholism in 642 patients,

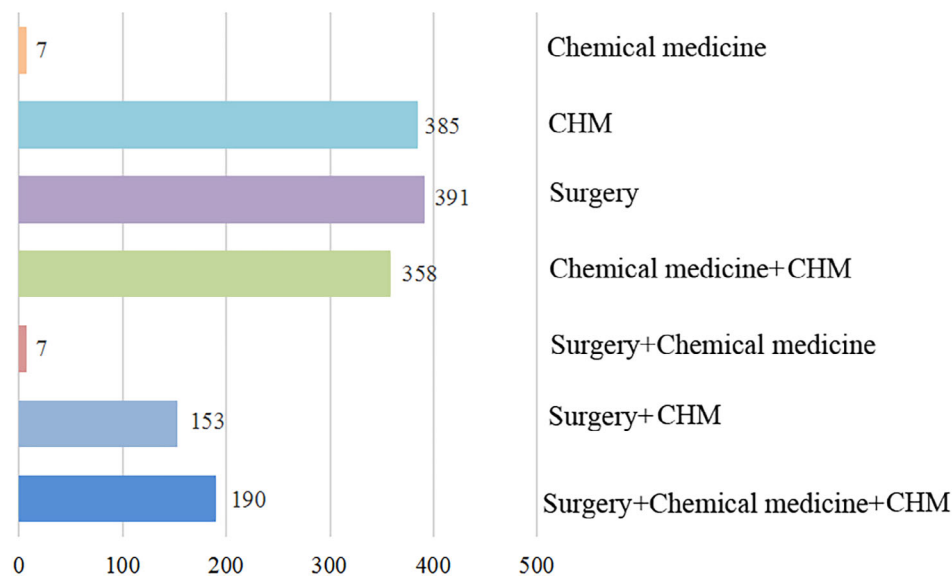


Fig. 2 Treatment regimens of the 1491 ONFH patients. CHM = Chinese Herbal Medicine.

TABLE 1 Utilization rate of different treatment regimens and modalities (%)

Category	Patient amount	Percentage (95%CI)	Hip amount	Percentage (95%CI)
Cases	1491	/	2381	/
Single regimen	783	52.5(50.0,55.1)	1130	47.5(45.5,49.5)
Combined regimen	708	47.5(44.9,50.0)	1251	52.5(50.5,54.5)
Operative treatment				
Alone	391	26.2(24.0,28.5)	576	24.2(22.5,25.9)
Total	741	49.7(47.2,52.2)	1028	43.2(41.2,45.2)
Chemical medicine				
Alone	7	0.5(0.1,0.8)	9	0.4(0.1,0.6)
Total	562	37.7(3.52,40.2)	927	38.9(37.0,40.9)
Chinese herbal medicine				
Alone	385	25.8(23.6,28.0)	616	25.9(24.1,27.6)
Total	1086	72.8(70.6,75.1)	1789	75.1(73.4,76.9)



Fig. 3 Operative treatments for the ONFH hips. (A) The amount of each surgical method used as single or combined regimen. (B) The amount of each surgical method used as single regimen. ARCO = Association Research Circulation Osseous.

long-term use of corticosteroid in 439 patients, a history of hip injury in 239 patients, and idiopathic ONFH in 171 patients. According to the Association Research Circulation Osseous (ARCO) classification¹⁵, 437 hips were classified as stage I (normal plain radiograph but with specific osteonecrosis findings on MRI), 761 hips as stage II (abnormal plain radiographs without collapse or a crescent sign), 706 hips as stage III (abnormal plain radiographs with collapse or a crescent sign), and 487 hips as stage IV (abnormal plain radiographs with hip arthritis). Detailed baseline characteristics of the participants were shown in Fig. 1.

Overview of the Treatment Regimens

Of the 1491 patients, 783 patients (1130 hips) were treated with single regimens, and the other 708 patients (1251 hips) received combined regimens of multiple interventions. As is shown in Fig. 2, the top three most used regimens were surgery, CHM, and a combination of chemical medicine and CHM. Surgery used alone, as well as the combination of surgery and chemical medicine, were rarely used when compared to other regimens.

Operative Treatments

Operative treatments were performed on 741 patients (1028 hips, Table 1 and Fig. 3), but these operative treatments were not always used alone (Table 2). A total of 576 hips were treated by surgery alone, and THA was the most used surgical method to be performed without other complementary treatments (506 hips). Among hips treated by surgery, all hips with ARCO stage IV ONFH received THA (305 hips), and THA was also performed on 63 hips with stage II.

Hip-preserving procedures were operated on 522 hips, but 452 of these hips were undergoing pharmacological

TABLE 2 Treatment regimens of the 2382 hips with ONFH (hips)

Intervention	Regimen	Regimen	ARCO stage I	ARCO stage II	ARCO stage III	ARCO stage IV	Total	
Operative treatment	Single regimen	Total hip arthroplasty	0	63	138	305	506	
		Bone grafting	6	26	14	0	46	
		Core decompression	10	14	0	0	24	
	Combined regimen	Bone grafting	88	131	39	0	258	
		Core decompression	41	121	23	0	185	
		Tantalum rod implantation	4	5	0	0	9	
	Total	Total hip arthroplasty		0	63	138	305	506
		Bone grafting		94	157	53	0	304
		Core decompression		51	135	23	0	209
		Tantalum rod implantation		4	5	0	0	9
Chemical medicine	Single regimen		6	3	0	0	9	
	Combined regimen		204	363	301	50	918	
	Total		210	366	301	50	927	
Chinese herbal medicine	Single regimen		96	206	214	100	616	
	Combined regimen		294	476	357	46	1173	
	Total		390	682	571	146	1789	

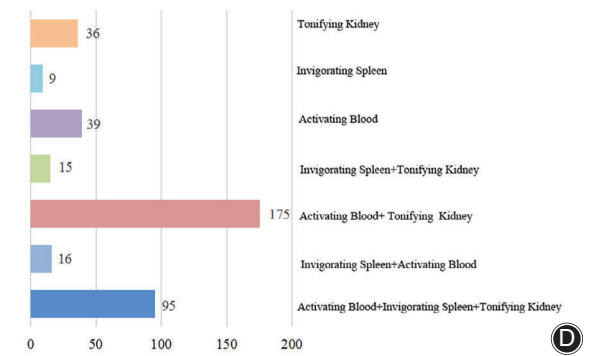
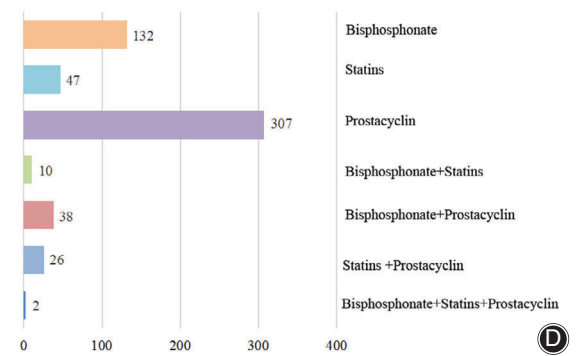
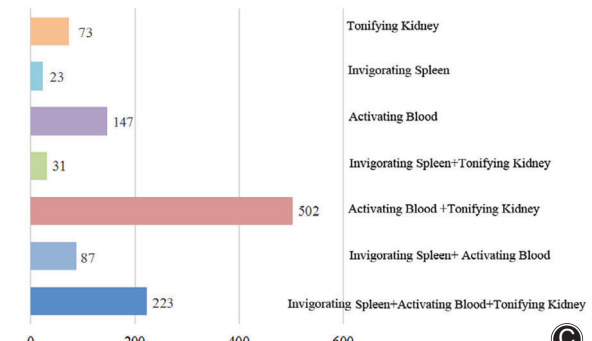
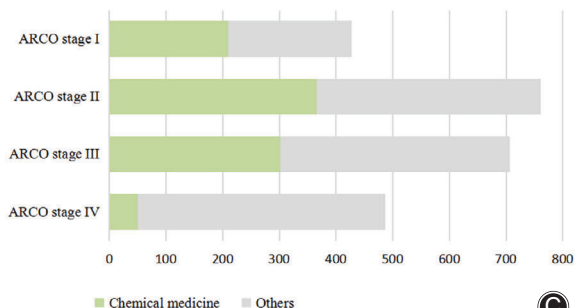
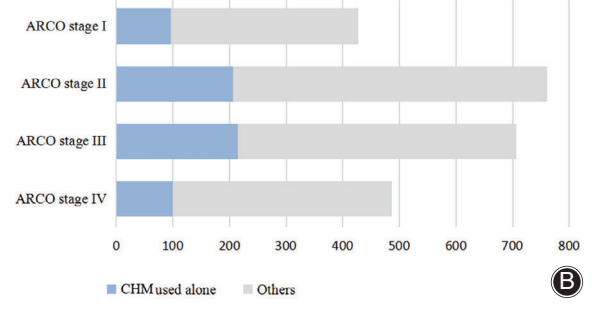
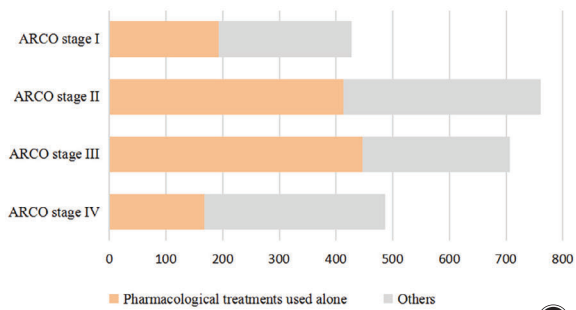
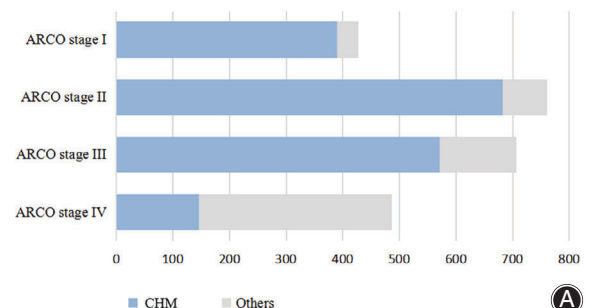
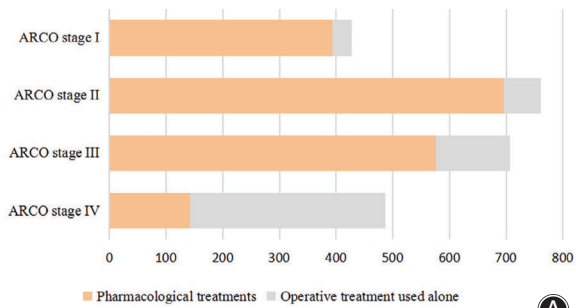


Fig. 4 Pharmacological treatments for the ONFH hips. (A) The amount of pharmacological treatments used as single or combined regimen. (B) The amount of pharmacological treatments used as single regimen. (C) The amount of chemical medicine used as single or combined regimen. (D) The amount of chemical medicine used alone categorized by the application ways. ARCO = Association Research Circulation Osseous.

Fig. 5 CHM treatments for the ONFH hips. (A) The amount of CHM used as single or combined regimen. (B) The amount of CHM treatments used as single regimen. (C) The amount of CHM used categorized by the application ways. (D) The amount of CHM used alone categorized by the application ways. ARCO = Association Research Circulation Osseous. CHM = Chinese Herbal Medicine.

treatments as well. Bone grafting and core decompression were the main procedures used for stage II hips (157 and 135 hips, respectively), but 76 hips (53 and 23 hips, respectively) with stage III ONFH also received these surgeries.

Pharmacological Treatments

Pharmacological treatments were prescribed to 1102 patients (1806 hips), and 750 of these hips (1220 hips) received pharmacological treatment as the single regimen. Over half of the hips with stage I, II, or III ONFH had received pharmacological treatments (Fig. 4A, single or combined regimens). Additionally, over half of the hips with stage II or III ONFH were treated by pharmacological treatments alone (Fig. 4B).

Chemical medicine treatment was given to 562 patients (927 hips), but 555 patients (918 hips) received chemical medicine treatment as complementary treatments for surgery or CHM. Only seven patients (nine hips) were prescribed with chemical medicine alone. Prostacyclin and bisphosphonate were the top two most prescribed medicine used alone while the combined use of prostacyclin, bisphosphonate, and statins was the least common prescription (Fig. 4D).

CHM Treatments

CHM therapies were administrated to 1086 patients (1789 hips), and the amounts of hips categorized by ARCO stage I to IV were 390, 682, 517, 146, respectively. Similarly, CHM was mainly used as complementary treatment with surgery or chemical medicine (1173 hips, Fig. 5A,B). Unlike surgical methods or chemical medicine, CHM therapies that contained herbs with different CHM functions were more commonly prescribed, including the combination of herbs with activating blood function and tonifying kidney function, and the combination of herbs with activating blood function, tonifying kidney function, and invigorating spleen function (Fig. 5C,D).

Discussion

The current study suggests that the treatment modalities for ONFH patients in mainland China include operative treatment, chemical medicine, and CHM. These treatment modalities are not always used alone. According to our study, 49% of patients (43% of hips) with ONFH received operative treatments, 72% of patients (75% of hips) had been undergoing treatment with CHM, 98% of chemical medicine was prescribed as a complementary treatment to operative treatment and (or) CHM.

Although no optimal operative treatment currently exists^{16, 17}, the indications for each surgical method is relatively unequivocal. THA is suitable for collapsed ONFH (ARCO stage III or IV) and hip-preserving procedures are suitable for pre-collapse ONFH (ARCO stage I or II). However, the utilization status of these operative treatments in clinical practices seems inconsistent with the established knowledge. In most cases, patients reserve the right to make the final decision. According to our data, only 62% of stage IV hips and 19% of stage III hips had undergone THA. It is

believed that patients with early-stage lesions (ARCO stage I or II) are more likely to acquire better outcomes if they received timely hip-preserving procedures. But we recorded that only 34% of stage I hips and 39% of stage II hips were subject to hip-preserving procedures. Even more noteworthy is that around 10% of stage III hips had undergone hip-preserving procedures and 8% of stage III hips had received THA.

Seldom marketed chemical medicine is approved to treat ONFH by the Food and Drug Administration across the world. Thus, the use of chemical medicine for ONFH in clinical practices is an off-label use. The use of chemical medicine is mainly based on the pathogenesis of ONFH that abnormal lipid metabolism¹⁸ and bone turnover¹⁹ are closely associated with the ischemia of the femoral head²⁰. Some previous clinical trials had demonstrated promising outcomes with the use of bisphosphonate²¹, statins²², and prostacyclin²³. Frustratingly, updated clinical trials reported negative results and suggested no chemical medicine is recommendable at this moment⁸. This may explain the fact that most chemical medicines were used as a complement to other treatments, according to this study.

Our data again confirmed the fact that a considerable number of ONFH patients in China prefer to seek TCM treatments rather than operative treatment or chemical medicine. About 70% of patients had been undergoing treatment using CHM, though over half of CHM was used as the complement to other treatments. In mainland China, the China Food and Drug Administration (CFDA) had approved several Chinese patent medicines for osteonecrosis, and CHM is also legitimate for ONFH if prescribed by TCM practitioners. In contrary to the operative treatment, CHM is noninvasive and less expensive. Previous animal testing had supported the use of CHM^{24, 25} to ameliorate the progression of ONFH. Scientific researchers had different attitudes towards the clinical effect of CHM, with most foreign guidelines not including TCM therapies, and CHM not always being accessible in the Western world.

The treatment decision-making process for young patients with post-collapse ONFH is the most difficult. Although updated data supported that THA is a reliable option with long-term implant survivorship and promising functional outcomes²⁶, young patients themselves are not always willing to remove their autogenous hips and accept THA due to potential complications, including dislocation and prosthetic fracture²⁷. Moreover, the implant lifespan is limited, but the expected human lifespan is growing with medical technology. Some Chinese experts offered a proposal that mild-collapse ONFH (stage-III) is still the indication for hip-preserving procedures²⁸. Data from our study reflected the neutral attitudes of clinical practitioners on this proposal. Our data found only 19% of stage-III hips had undergone THA, and 10% of stage-III hips had received hip-preserving procedures. Interestingly, 80% of stage-III hips had been undergoing CHM therapy since the effect of hip-preserving treatments is controversial²⁹, and THA is not acceptable for young patients.

The present study had several limitations. First, it is estimated that there are over 8 mn patients suffering from ONFH in mainland China¹⁰, but the current study only investigated 1491 patients. Second, there are 34 administrative areas (provinces or municipalities) in China, and this study only included patients from 12 administrative areas. Lastly, this study only includes patients who can cease corticosteroid therapy or other treatments for the primary disease, or abstain from alcohol. Hence, our results can not fully represent the nationwide status. Nevertheless, this study might be the first to investigate the implementation of the recommended treatments of Chinese guidelines. Our data was still sufficient in reflecting

the complicated situation in real-world practices, and future research is thus necessitated to re-evaluate the effect and safety of the combined use of different interventions.

In conclusion, treatment modalities for ONFH patients in mainland China include operative treatment, chemical medicine, and CHM. According to the present study, the most commonly used modality is CHM. Hip-preserving procedures were always used as a combined regimen with pharmacological treatment. Chemical medicine is frequently used as a complementary treatment. Future guideline works shall draw attention to addressing the problems of combined-treatment regimens.

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