10-year Follow-up of the Prospective, Double-blinded, Randomized, Controlled Study of Autologous Bone Marrow Buffy Coat Grafting Combined With Core Decompression in Patients With Avascular Necrosis of Femoral Head

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Abstract

Background: Avascular necrosis of femoral head (ANFH) is a severely disabling disease of hip.Several clinical trials have shown promising outcomes on the use of mesenchymal stem cells for treatment of ANFH but long-term clinical assessment is lacking. Previously we have reported two year follow up of a prospective, double-blinded, randomized, controlled study of autologous bone marrow buffy coatgrafting combined with core decompression in patients with ANFH. Here we reported the outcome of ten year follow up on the study.

Methods: We recruited 43 (53 hips) patients from 2009 to 2010. The hips were randomly allocated to code decompression (CD) with and without bone marrowbuffy coat (BBC). Participants were followed at 24, 60, 120 months postoperatively. Visual analogue scale (VAS), Lequesne algofunctional index and Western Ontario and McMaster Universities Arthritis Index (WOMAC) osteoarthritis scoring were recorded. Survival rate analysis and the prognostic factor analysis were performed. The endpoint was defined as progression to Ficat stage IV or conversion to hip arthroplasty.

Results: 31 patients (41 hips) were included in the final analysis. CD + BBC group scored better in subjective assessing scores compared with CD group. The average survival time was 102.3 months and 78.1 months for CD + BBC group and CD group, respectively (Log-rank test, $P = 0.029$). In the univariate COX proportional-hazards regression model, age [hazards ratio (HR) = 1.079, $P = 0.047$] and pre-operative Ficat stage (HR = 3.283, $P = 0.028$) indicated high risk for progression, while the use of BBC (HR = 0.332, $P = 0.042$) indicated low risk. Pre-operative Ficat stage IIIwas isolated as an independent risk factor for clinical failure in the multivariate model (HR = 3.743, $P = 0.018$).

Conclusion: The outcome of ten year follow up on this prospective, double-blinded, randomized,controlled study showed that use of the autologous BBC in combined with core decompression is more effective than core decompression alone.

TrialRegistration: ClinicalTrials.gov identifier NCT01613612. Registered 13 December 2011 – Retrospectively registered, https://clinicaltrials.gov/ct2/show/record/NCT01613612.

Background

The etiology of avascular femoral necrosis of femoral head (ANFH) is multi-factorial, including trauma, corticosteroid use, excessive alcohol consumption[1]. ANFH is often initiated with impaired circulation of the femoral head, leading to ischemia by increased intraosseous pressure and consequently causing osteonecrosis of subchondral plate necrosis and osteoarthritis. Because ANFH is progressive and eventually leads to hip dysfunction and disability, total hip arthroplasty (THA) is the ultimate treatment for terminal ANFH. Nonetheless, despite the success of primary THA, recent registry data revealed that the revision burden was 4.7 ~ 13.8%, which implicates the poor prosthetic durability[2]. Therefore, concerns are growing about hip joint preservation prior to subchondral bone collapse, especially for those younger and physically demanding individuals. Conservative procedures, in terms of core decompression and

vascularized or avascular bone transplantation have been widely used for the early stage ANFH in order to delay the pathological progression, and several clinical researches showed favorable short-term and mid-term results[1]. Core decompression, which can directly mitigate intraosseous hypertension, is the most common treatment because of its advantage of minimal invasion. However, the efficacy of traditional core decompression is inconsistent. Some short-term studies indicated that the clinical failure rate reached 20 ~ 70% even for those in the early stage (Ficat stage I/II). Bone-grafting strategy was employed to provide subchondral structural support to allow healing and remodeling[3]. Based on the current literature, bone-grafting can postpone femoral head collapse and reserve hip joint function. However, this procedure is more invasive and can lead to donor site morbidity and nerve palsy.

In the last decade, accumulating evidence indicated that a decreased pool of osteoprogenitor cells in the bone marrow of the femoral head is associated with the etiology of ANFH. Thus, there has been enthusiasm for applying osteogenic precursors into necrotic lesion of ANFH[4]. With the use of cell therapy such as mesenchymal stem cells (MSCs) transplantation or bone marrow aspirate concentrate injection, previous published reports have demonstrated the benefits, including significant pain relief, reduced time to collapse, decreased lesion sizes and functional restoration[5–7]. Although some of the studies had high evidence level, the follow-up time was relatively short[3, 8–13]. There is a lack of long-term data evaluating the efficacy. Previously we have reported the outcome of two year study showing that implantation of the autologous bone marrow aspirate, the concentrate bone marrow buffy coat (BBC) combined with core decompression is promising in pain relieving and postponing THA[3]. In the present study, we continue the follow up of this prospective, randomized, controlled trial to further investigate the longer-term outcome of the study. We report the 10-year outcome showing that use of the autologous BBC in combined with core decompression is more effective than core decompression alone.

Methods

Study design

This study design was approved by the Institutional Review Board of Guangdong Provincial People's Hospital and was performed in strict accordance with the ethical standards stipulated in the 1964 Declaration of Helsinki and its later amendments. Signed informed consent for participation was obtained from all study patients. The trial protocol was submitted to ClinicalTrials.gov, and the trial registration number is NCT01613612.

Based on the results of Gangi et al[14], we determined that at least 20 patients per group were necessary to detect the difference by using Wilcoxon-Mann-Whitney test with a bilateral α of 0.017 and a power of 80%. We included a minimum of 26 patients in each group in order to compensate the patients lost to the follow-up.

Patients

We recruited the eligible patients from those administrated in the Center of Orthopedics Surgery from June 2009 to October 2010. Plain radiograph of bilateral hips at the anteroposterior and frog-leg lateral positions and magnetic resonance imaging (MRI) were taken for all patients. We confirmed the diagnosis of ANFH based on the clinical history and the radiographic lesions in the femoral head.

Inclusion criteria were as follows: the subjects (1) were 18 to 55 years old; (2) had notable hip pain; (3) had normal, minor, or mixed osteopenia or were detected the presence of crescent sign in the plain radiograph; (4) stopped steroid treatment for at least 6 months.

Exclusion criteria were included: (1) < 18 or > 55 years old; (2) terminal stage of ANFH with the presence of secondary osteoarthritic changes such as osteophyte formation, narrowed joint gap, osteosclerosis, etc.; (3) history of fracture in the proximal femur, tumor and any other concomitant lower extremity diseases; (4) previous history of any surgical treatment in terms of core decompression, bone-grafting, titanium implantation, osteotomy; (5) inflammatory arthritis, including rheumatoid arthritis, suppurative arthritis and gouty arthritis; (6) having received steroid treatment in the last 6 months; (7) pregnancy.

After meeting the inclusion criteria, we provided the informed consent to the participants and assessed their baseline characteristics. The hips were randomly allocated to receive core decompression (CD) + autologous bone graft (BG) or core decompression + autologous bone graft + BBC (CD + BG + BBC) by a randomization schedule, which was generated by computer-based block randomization.

Surgical Technique

All surgical procedures were performed under continuous epidural anesthesia. For core decompression of the femoral head, we firstly determined the optimal entrance point for drilling, and then a 1.5-cm incision was made at the level of the greater trochanter. A 3.0 mm diameter Kirschner wire (k-wire) was introduced toward the necrotic area with the tip placed at the subchondral bone area approximately 2 to 3 mm from the articular cartilage. Next, a 10-mm diameter trephine was drilled through the k-wire to the necrotic region. A cylinder of bone from the femoral neck and head was obtained. The necrotic proximal part was eliminated and the healthy part was used for BBC grafting. The necrotic tissue remained in the femoral head was removed by the bone curette. All the above steps were performed under C-arm X-ray guidance.

For bone marrow collection, a 50-mL syringe, heparinized in advance, was used to harvest the bone marrow from the superior posterior iliac spine. Bone marrow was centrifuged at 1500 revolutions per minute for 10 minutes in a bench-top centrifuge (Ependoff, AG 22331, Hamburg, Germany) with a sterilized chamber. The bone marrow was separated into three phases after centrifuge. We collected a total of 1 mL of bone marrow concentrate from the interface containing enriched bone marrow cells by a sterilized transfer pip pet, and then bone marrow concentrate was seeded on the cylindrical bone drop by drop in order to allow the cells to anchor on the bone surface. 10 μL of bone marrow concentrate was kept for cell counting after the surgery. The average bone marrow cells loaded to the cylindrical bone were approximately 3×10^9 nucleated cells.

The bone graft with or without BBC was inserted into the necrotic region with the guidance of C-arm X-ray. After surgery, the patients were instructed to remain non-weight-bearing for 4 weeks. Surgical complications were monitored after operation.

Outcome Assessment

Preoperatively, the blinded evaluators collected the baseline demographic information, including age, sex, etiological factors, presurgical Ficat stage of ANFH, and location of defect. Plain X-ray radiograph and MRI were used to determine Ficat stage of ANFH and the location of necrotic lesion. All participants were followed at 24, 60, 120 months postoperatively. Anteroposterior and frog-leg lateral radiographs were taken at each time of clinical assessment. Radiographic progression of the ANFH was determined based on Ficat classification system. The primary outcomes included visual analogue scale (VAS), Lequesne algofunctional index and Western Ontario and McMaster Universities Arthritis Index (WOMAC) osteoarthritis scoring. Secondary outcome was the clinical failure rate of the operated hips at 5 years and at the time of the final follow-up. The clinical failure rate was defined as the proportion of hips that progressed to Ficat stage IV or subjected to THA.

Statistical analysis

The SPSS 22.0 software package (IBM Inc. USA) was used for statistical analysis. The data was described as median, maximum and minimum value. Chi-square test and Fisher's exact test were used for categorical variables. The statistical significance of demographic data and functional assessments between two groups were determined by Wilcoxon-Mann-Whitney test. The clinical survival was compared between each group with Kaplan-Meier survivorship analysis and the statistical significance was determined by log-rank test. COX proportional-hazards regression model was employed to detect the risk factors affecting the survival of femoral head. The level of statistical significance for all tests was defined at $P < 0.05$.

Results

Demographic and baseline characteristics

77 patients (94 hips) were screened for eligibility. After excluding 34 patients (41 hips), 43 (53 hips) patients met the inclusion criteria were recruited and randomly allocated into CD + BG and CD + BG + BBC group. A total of 12 patients (12 hips) were lost during follow-up time. In the CD + BG group, 3 patients lost contact and 3 patients quit this trial for personal reasons. In the CD + BG + BBC group, 2 patients lost contact and 4 patients left the study for personal reasons. 31 patients (41 hips) were included in the final analysis (Fig. 1). Table 1 showed the demographic data and clinical baseline characteristics of the included subjects. The data of the two groups was homogeneous.

Table 1
Demographic and baseline data of included patients

	CD + BC group (n = 14)	CD + BC + BBC group (n = 17)	P value
Number of hips	20	21	
Age, years	38.2 ± 8.1	34.1 ± 8.0	0.112
Sex			1.000
Male	10	12	
Female	4	5	
Etiology			0.900
Steroid	9	10	
alcohol	5	6	
idiopathic	6	5	
Ficat Stage			0.867
II	11	11	
III	9	10	
VAS	4.5 (2 to 10)	4 (2 to 10)	0.703
Lequesne index	10 (3 to 20)	9 (1 to 21)	0.539
WOMAC	33 (8 to 91)	21 (2 to 80)	0.179

SD: standard deviation; CD: core decompression; BG: bong grafting; BBC: bone marrow buffy coat; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index osteoarthritis scoring

Functional Outcomes Changes During Follow-up

The VAS score was significantly lower in the CD + BG + BBC group at each follow-up time point post-operatively compared with CD + BG group (24-month: $P = 0.028$; 60-month: $P = 0.018$; 120-month: $P = 0.001$, respectively). In terms of Lequesne index, the CD + BG + BBC group scored significantly better 24-month ($P = 0.005$), 60-month ($P = 0.001$) and 120-month ($P = 0.001$) post-operatively than CD + BG group. The WOMAC score was significantly lower in CD + BG + BBC group than that in CD + BG group at 24-month ($P = 0.010$) and 120-month ($P < 0.001$) after surgery (Table 2; Fig. 2). 4 patients in the CD + BG group undergone THA, while 2 patients in the CD + BG + BBC group proceeded to THA.

Table 2
Functional outcomes [mean (min to max)] before and after surgery

		Pre-operation	24 months post-operation	60 months post-operation	120 months post-operation
VAS	CD + BC	4.5 (2 to 10)	3 (1 to 5)	4 (1 to 6)	3.5 (1 to 7)
	CD + BC + BBC	4 (2 to 10)	3 (1 to 4)	3 (0 to 4)	1 (0 to 5)
P value		0.703	0.028	0.018	0.001
Lequesne index	CD + BC	10 (3 to 20)	7.5 (3 to 11)	6.5 (3 to 13)	9 (0 to 18)
	CD + BC + BBC	9 (1 to 21)	6 (0 to 8)	4 (1 to 6)	4 (0 to 12)
P value		0.539	0.005	0.001	0.001
WOMAC	CD + BC	33 (8 to 91)	26 (4 to 43)	14.5 (8 to 36)	32.5 (2 to 72)
	CD + BC + BBC	21 (2 to 80)	18 (3 to 27)	12 (0 to 24)	8 (1 to 31)
P value		0.179	0.010	0.131	< 0.001

SD: standard deviation; CD: core decompression; BG: bong grafting; BBC: bone marrow buffy coat; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index osteoarthritis scoring

Survivorship During Follow-up

CD + BG + BBC group showed a clinical failure rate of 14.3% (3/21) at the 5 years follow-up, and the figure in CD + BG group was 40.0% (8/20). The Fisher's exact *P* value was 0.065. At the final follow-up, the clinical failure rate was 23.8% (5/21) in the CD + BG + BBC group and 50.0% (10/20) in the CD + BG group with the Fisher's exact *P* value of 0.078. There was a significant difference between the two groups with respect to the addition of BBC (Log-rank test, $P = 0.029$) using Kaplan-Meier survival analysis (Fig. 3). The average survival time was 102.3 months and 78.1 months for CD + BG + BBC group and CD + BG group, respectively.

Univariate COX regression analysis (Fig. 4) showed that age [hazards ratio (HR) = 1.079, $P = 0.047$], pre-operative Ficat stage (HR = 3.283, $P = 0.028$) and the addition of BBC (HR = 0.332, $P = 0.042$) were significantly associated with the survivorship for the total of 41 hips. After included the aforementioned three factors in the multivariate COX regression analysis (Fig. 4), we found only the Ficat stage of ANFH showed significant association with the survivorship (HR = 3.743, $P = 0.018$). Pre-operative Ficat stage III hips increased the risk of progression by 2.743 times compared with Ficat stage II hips.

Discussion

Since its initial proposal by Hernigou[15], the injection of bone marrow aspirate concentrate through the core decompression tunnels was employed in more than 20 clinical researches[16]. Although the current literature included Level I and Level II evidence, the follow-up period of 2 to 5 years was relatively short. The current prospective, randomized, controlled study supported the hypothesis that the surgical procedure that combined CD, autologous bone grafting and BBC led to a significantly higher survival rate on a long-term basis. It was consistent with Hernigou's previously published result that 72% (80/114) of hips after bone marrow grafting survived at an average of 25-year follow-up while 76% (95/125) of hips treated with single core decompression collapsed[15]. The utilization of BBC also improved the functional outcomes compared with CD plus bone grafting, which is in accordance with the latest systemic review and meta-analysis[5–7].

CD, which works by drilling single or multiple tunnels from the greater trochanter, through the femoral neck, to the subchondral lesion of the femoral head, is most commonly performed minimal invasive procedure for pre-collapse ANFH. It is potentially beneficial for relieving the increased bone pressure, and thus promotes healing of the femoral head[17]. However, CD might deprive the subchondral mechanical support as well as the quantity and quality of the regional MSCs, thereby leading to insufficient bone remodeling and angiogenesis. This is corresponded by the result that clinical failure of single CD reached as high as 30% even for Ficat stage I/II ANFH hips[4, 17]. In the present study, we used the healthy part of autologous cancellous bone that was obtained from greater trochanter and femoral neck to enhance the subchondral mechanical support.

MSCs are desirable in the treatment of ANFH because of their capacity for multipotent differentiation. The purpose of adding MSCs into the core decompression tunnel is to provide osteoprogenitor and vascular progenitor cells to the area of decompressed necrotic bone, in order to facilitate tissue regeneration and repair[18]. Among the various types of MSCs, bone-marrow derived MSCs (BM-MSCs) are most commonly used because of its superiority in bone and cartilage repair. Additionally, BM-MSCs can release exosomes that contain cytokines promoting osteogenesis, chondrogenesis and angiogenesis, including bone morphogenetic protein-2, vascular endothelial growth factor, transforming growth factor-beta[4, 19, 20]. As was used in other published researches, we utilized BBC as the source of BM-MSCs, which was technically easy to harvest and had no need to culture ex vivo. Aside from BM-MSCs, BBC contains endothelial progenitors and hemangioblasts that contribute to vessel reconstruction, and thus improve the avascular micro-environment. Based on the current literature[5, 15], the reasonable cell number for treatment ranged from 10^6 to 10^9, so BBC containing 10^9 nucleated cells in the present cohort was suitable in this cell therapy.

In the present study, we detected the prognostic factors using COX proportional-hazards regression model. In the univariate model, age and pre-operative Ficat stage indicated high risk for progression, while the use of BBC indicated low risk. Nonetheless, only pre-operative Ficat stage was isolated as an

independent risk factor in the multivariate model. This result is in line with the current literature that collapse stage lesion showed a worse survival rate compared with pre-collapse stage[9, 11–13, 21, 22]. It may be attributed to the decreased replication and increased apoptosis rate of osteoblasts and osteocytes in Ficat stage III femoral head[17]. From a molecular aspect, Ying et al[23] reported a high inflammatory cytokines level in the femoral head while significant microfracture was detected. Therefore, larger number of MSCs may be necessary to treat advance lesions. Age-related atrophy of MSCs has been reported as a cause of decreased number and capacity of differentiation of MSCs, leading to decreased bone formation[24]. However, the hazard-ratio of age was not significant in our multivariate model. Additionally, patients with ANFH secondary to steroid use and alcoholism had impaired MSCs activity and etiology was considered as a prognostic factor for hip-preservation[4, 25], but it failed to be isolated in our model. Given the small number of patients, future studies with larger sample sizes may give insights.

This study had some limitations. First, the number of patients included in the final analysis was small aforementioned, so we did not perform subgroup analysis with respect of etiology. Secondly, we included the patients of bilateral ANFH, so the potential similar performance of bilateral hips may lead to a contralateral effect related to the cell therapy. Thirdly, we did not obtain the MRI images post-operatively, which interfered the accuracy of staging. Last but not least, there was a lack of evidence of the fate and track of the implanted cells, so cell labelling technique would be beneficial.

Conclusion

The ten year follow up of this prospective, double-blinded, randomized, controlled study showed that use of the autologous BBC in combined with core decompression is more effective than core decompression alone. Pre-operative Ficat stage is an independent risk factor for predicting the post-operative survival rate. Ficat stage III hips have a higher risk for progression.

Declaration

List Of Abbreviations

ANFH, Avascular femoral necrosis of femoral head

THA, Total hip arthroplasty

MSC, Mesenchymal stem cell

BBC, Bone marrow buffy coat

CD, core decompression

BG, bone-grafting

HR, hazards ratio

VAS, Visual analogue scale

WOMAC, Western Ontario and McMaster Universities Arthritis Index osteoarthritis scoring

Declarations

Acknowledgments

Not applicable.

Authors' contributions

Study design: Minghao Zheng, Qiujian Zheng.

Administrative support: Yuanchen Ma, Qiujian Zheng.

Surgery performance: Yuanchen Ma.

Study conduct: Mengyuan Li, Yuanchen Ma.

Data collection: Mengyuan Li, Ruiying Zhang.

Data analysis and data interpretation: Mengyuan Li, Qingtian Li, Zhantao Deng.

Drafting manuscript: Mengyuan Li, Guangtao Fu.

Revising manuscript content: Mengyuan Li, Minghao Zheng, Qiujian Zheng.

Approving final version of manuscript: Minghao Zheng, Qiujian Zheng. Minghao Zhengand Qiujian Zheng takes responsibility for the integrity of the data analysis.

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Availability of data and materials

Thedataandmaterials used and/or analyzed during the current study are not publicly available but available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The presentstudy was approved by the institutional review board ofGuangdong Provincial People's Hospital and signed informed consent for participation was obtained from all study patients.The trial protocol was submitted to ClinicalTrials.gov, and the trial registration number is NCT01613612.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

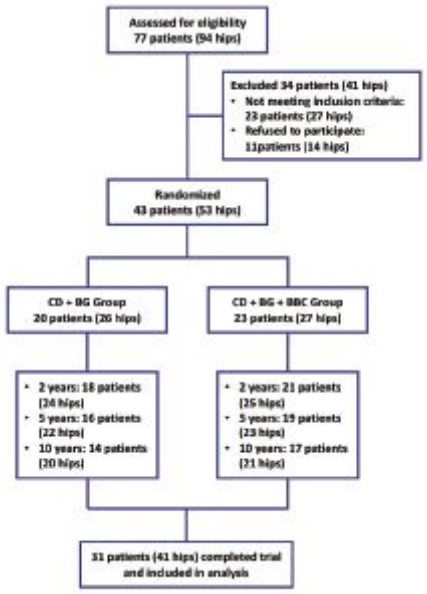

Figure 1

Flowchart of the present study (CD: core decompression; BG: bong grafting;BBC: bone marrow buffy coat)

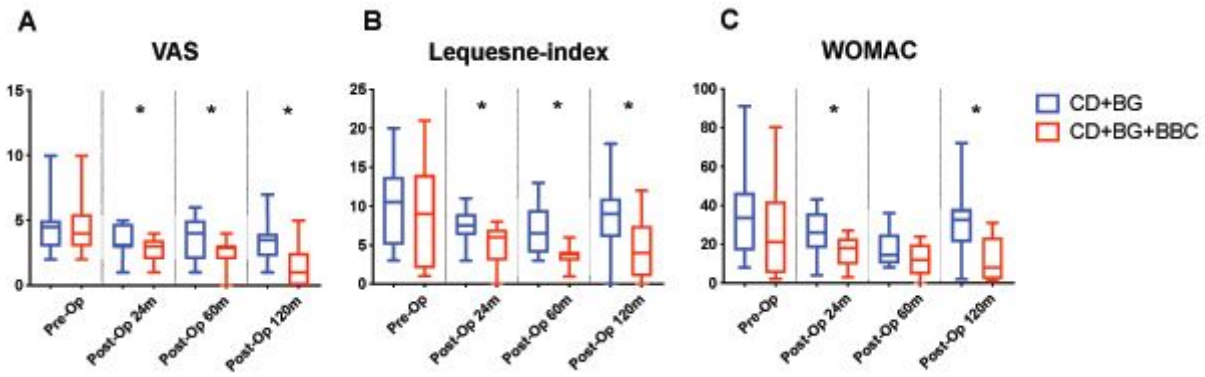

Figure 2

Functional outcome before and after surgery. Error bars denote the minimum and maximum valueof each group.Segments with significant statistical differences (*: P<0.05)between the groups were marked with asterisks. (CD: core decompression; BG: bong grafting;BBC: bone marrow buffy coat; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index osteoarthritis scoring)

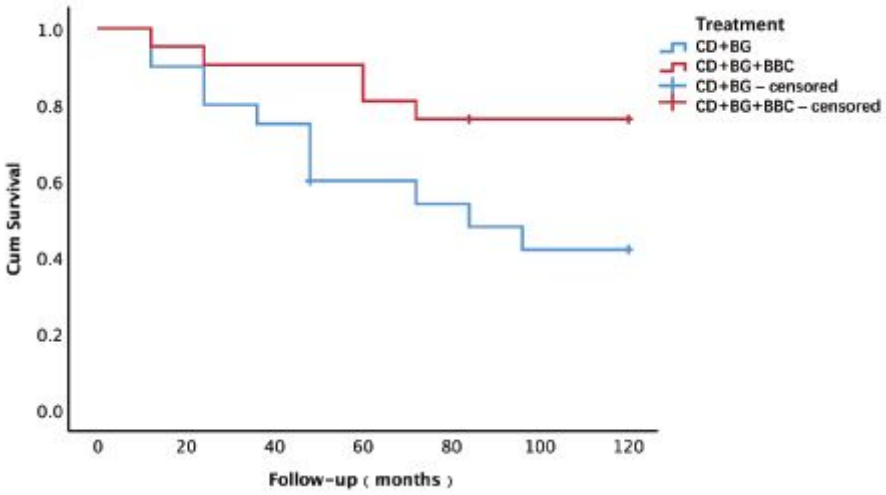

Figure 3

Kaplan-Meier survival curve showing femoral head survival dependent on the treatment. (CD: core decompression; BG: bong grafting;BBC: bone marrow buffy coat)

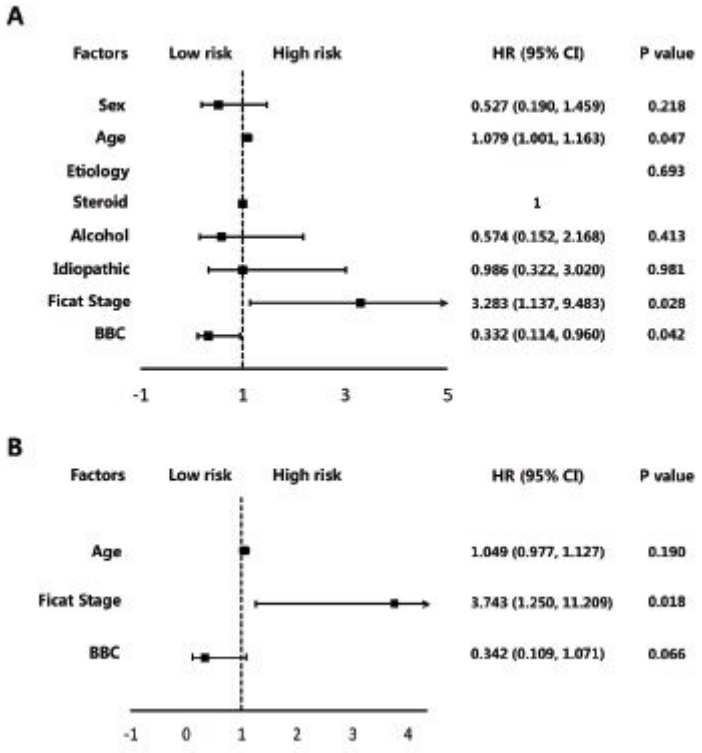

Figure 4

Univariate and multivariate COX proportional-hazards regression analysis. The forest plot of hazard ratio showed the proportional risk. (BBC: bone marrow buffy coat; HR: hazard ratio; CI: confidence interval)