

Peer Review File

Article information: <http://dx.doi.org/10.21037/atm-20-4866>

Reviewer

Comment 1) The occurrence of femoral head necrosis was significantly related to removal of internal fixation, fracture classification, age, gender and postoperative weight bearing time. What impact do these factors have on the research model?

Reply 1) Thanks for your kind comment. Regarding the removal of internal fixation, its effect on femoral head necrosis remains controversial [1]. In recent years, several studies have advocated that retention of internal fixation reduces the risk of re-fracture and necrosis, including a recent meta-analysis [2]. Therefore, in these two centers, we advocate that patients should not remove internal fixation as much as possible after canulated screws fixation. At the same time, as two central hospitals, some of our patients received removal operation in their local hospitals, thus, we could not accurately collect information about the intraoperative conditions. Therefore, the variable of removal of internal fixation was not adopted by us. We will also explain this variable in the discussion.

Regarding fracture classification and postoperative weight bearing time, they were significantly associated with the development of osteonecrosis. In fact, in our study, we did regression analysis of Garden classification, Pauwels classification, postoperative partial weight-bearing time and postoperative full weight-bearing time. Garden classification and postoperative partial weight-bearing time were also adopted as variables in the final nomogram model. Although other factors also have predictive significance, we tend to minimize the number of variables in nomogram, when the existing model has been able to provide sufficient prediction accuracy and potency.

Age and gender are always considered playing important roles in predicting osteonecrosis. However, neither our study nor other studies including meta-analysis have found the predictive value of these two factors [2]. In our opinion, this is

because we have screened patients for these two factors before surgery. Especially for the elderly patients, joint replacement is chosen as the surgical method in most cases. Therefore, age and gender were no longer variables for all patients with femoral neck fractures in the final included population, but those who had undergone internal fixation and were generally considered to be under 65 years of age. We will also explain these variables in discussion.

Change in the text 1) we have discussed these topics in discussion (see line 353-365)
Some factors were not included in our study because of controversial concepts. For example, in recent years several studies have suggested retaining internal fixation as a way to reduce the incidence of refracture and necrosis [2]. We also recommend in clinical practice that patients should avoid removal of internal fixation, resulting in minimal amount of removal surgeries. At the same time, some patients received removal surgery in local hospitals, which made it difficult for us to collect necessary surgical information. A few factors have no clear predictive value because of pre-screening in the hospitals. For example, age and gender were not significant predictors in either our study or other studies. This may be due to elder patients tend to undergo arthroplasty, leading to the fact that the population included in these studies were already in a specific age and gender range, so these variables had no positive effect.

Comment 2) This study lacks external verification.

Reply 2) Thanks for your kind comment. The study was based on patients at two trauma centers. In order to avoid bias when develop a predictive model based on single center patients, we randomly selected patients in both centers during regression analysis, model construction and validation. Therefore, both in the training cohort and in the internal validation cohort, our data covered patients from both centers who were randomly assigned. This can reflect the stability and applicability of the model. Of course, the presence of a third hospital as an external validation queue may provide evidence of the applicability of the model. However, unfortunately we don't have data yet on the third hospital. This will be discussed as a limitation and implemented in

future prospective multicenter studies.

Change in the text 2) we have discussed these topics in discussion (see line 378-384)

Second, our study was lack of external validation for the nomogram model. Although the data of patients from two independent hospitals were randomly assigned in the establishment and validation of the nomogram model, our results also showed the stability and applicability of the model, but it would be better if a third hospital could be used as external validation cohort. A prospective multicenter study is proceeding.

Comment 3) How to reduce the probability of femoral head necrosis?

Reply 3) Thanks for your kind comment. There are many ways to reduce the probability of necrosis, including but not limited to: for patients with high risk of necrosis predicted by the model, joint replacement can be directly selected in combination with their own wishes to avoid the occurrence of necrosis; For patients with high predictive value due to fracture pattern factors, special reduction techniques, open reduction and more stable fixation methods such as buttress plate or FNS can be utilized to improve the score of fractures reduction and reduce the probability; As for the high predictive value caused by other factors, the time of full-weight bearing can be delayed to reduce the probability. Although there is no direct evidence that delayed full-weight bearing reduces the probability of necrosis, early full-weight bearing may increase this probability [3]. We also made some supplementary explanation in discussion.

Change in the text 3) we have discussed these topics in discussion (see line 378-384)

For examples, among patients with high risk of necrosis predicted by the model, joint replacement can be directly selected in combination with their own wishes to avoid the occurrence of ONFH. As for patients with high predictive value due to fracture pattern factors, special reduction techniques, open reduction and more stable fixation methods such as FNS can be utilized to improve the score of fractures reduction and reduce the probability. In addition to predicting the preoperative risk factors for ONFH, intervention can be carried out in the postoperative variable such as weight bearing, according to the preoperative score of the patient.

Comment 4) There are uncontrollable differences in internal fixation techniques, types and brands in surgery and between different centers. How to solve this problem?

Reply 4) Thanks for your kind comment. Two different hospitals have been used in the establishment and validation of the model, and the surgical techniques and internal fixation brands adopted by the two independent centers are different. For example, one hospital may use Zimmer's canulated screws, and another used Smith & Nephew canulated screws. In fact, not only in two hospitals, but also different patients in the same hospital will have difference in location of internal fixation and choose different lengths of canulated screws. Our consistency test showed that the stability and applicability of the model are good, indicating these uncontrollable differences may affected slightly to this predictive model. Meanwhile, a recent study found that the location differences under the implemented operations standard for the same fixation construct do not significantly affect the outcome [4]. Of course, the presence of a third hospital as an external validation queue may provide evidence of the applicability of the model. However, unfortunately we don't have data yet on the third hospital. This will be discussed as a limitation and implemented in future prospective multicenter studies.

Change in the text 3) we have discussed these topics in discussion (see line 378-384)
Third, some controversial and uncontrollable variables were not included in the study. This is because these variables are either practically uncontrollable or have been proven to be invalid variables, such as removal of internal fixation, surgery technique difference and various brands and location of the internal fixation. A recent study found that the location differences under the implemented operations standard for the same fixation construct do not significantly affect the outcome.

Comment 5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “A Study on the Evaluation of a Risk Score of Osteonecrosis of the Femoral Head Based on Survival Analysis, J Arthroplasty, PMID: 32800435”. It is recommended to quote this article.

Reply 5) Thanks for your kind comment. We have modified the introduction for better comprehension and cited some similar papers, such as “A Study on the Evaluation of a Risk Score of Osteonecrosis of the Femoral Head Based on Survival Analysis, J Arthroplasty, PMID: 32800435”.

Change in the text 5) we have cited the reference in introduction (see line 378-384)

A large number of studies had been performed using preoperative patient risk factors to predict ONFH after internal fixation [5]. Satisfactory results were obtained in these studies.

Comment 6) There are many uncertainties in retrospective research, which increase the deviation of research results. How to explain and solve this problem?

Reply 6) Thanks for your kind comment. This study was a retrospective cohort study and the selection bias cannot be ruled out. This problem is hard to solve and we have discussed it in limitation. In addition, Retrospective studies are prone to data fragmentation, and we have already recorded data by two doctors separately to avoid data errors. The problem of loss of follow-up in the retrospective study was resolved when we selected the study population, and patients lost to follow-up were excluded. As the two hospitals are teaching hospitals, there are strict rules in operation and diagnosis and treatment, and other confounding factors may be avoided as far as possible. Meanwhile, a multicenter prospective study is under way to address the issues raised by retrospective studies. We have discussed them in the limitation.

Change in the text 6) we have cited the reference in introduction (see line 378-384)

This study had some limitations. First, it was a retrospective cohort study and the selection bias cannot be ruled out. Due to the limited incidence of the disease in the population, the sample size and time of follow-up were slightly insufficient. A prospective multicenter study is proceeding.

Comment 7) There are many uncontrollable variables in this study. Please describe in the discussion.

Reply 7) Thanks for your kind comment. We have described them in the discussion in

revised manuscript.

Change in the text 6) we have cited the reference in introduction (see line 378-384)

Some factors were not included in our study because of controversial concepts. For example, in recent years several studies have suggested retaining internal fixation as a way to reduce the incidence of refracture and necrosis. We also recommend in clinical practice that patients should avoid removal of internal fixation, resulting in minimal amount of removal surgeries. At the same time, some patients received removal surgery in local hospitals, which made it difficult for us to collect necessary surgical information. A few factors have no clear predictive value because of pre-screening in the hospitals. For example, age and gender were not significant predictors in either our study or other studies. This may be due to elder patients tend to undergo arthroplasty, leading to the fact that the population included in these studies were already in a specific age and gender range, so these variables had no positive effect.

Third, some controversial and uncontrollable variables were not included in the study. This is because these variables are either practically uncontrollable or have been proven to be invalid variables, such as removal of internal fixation, surgery technique difference and various brands and location of the internal fixation.

[1] Wang T, Sun JY, Zha GC, Jiang T, You ZJ, Yuan DJ. Analysis of risk factors for femoral head necrosis after internal fixation in femoral neck fractures. *Orthopedics*. 2014;37:e1117-23.

[2] Xu JL, Liang ZR, Xiong BL, Zou QZ, Lin TY, Yang P, et al. Risk factors associated with osteonecrosis of femoral head after internal fixation of femoral neck fracture:a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2019;20:632.

[3] Kaushik A, Sankaran B, Varghese M. To study the role of dynamic magnetic resonance imaging in assessing the femoral head vascularity in intracapsular femoral neck fractures. *Eur J Radiol*. 2010;75:364-75.

[4] Li J, Wang M, Zhou J, Zhang H, Li L. Finite element analysis of different screw constructs in the treatment of unstable femoral neck fractures. *Injury*.

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[5] Zheng J, Wang H, Gao Y, Ai Z. A Study on the Evaluation of a Risk Score of Osteonecrosis of the Femoral Head Based on Survival Analysis. *J Arthroplasty*. 2020.