ORIGINAL ARTICLE

Dynamic changes and clinic significance of serum high mobility group box 1 in patients with total hip arthroplasty

Cambios dinámicos y significado clínico de la HMGB1 sérica en pacientes con artroplastia total de cadera

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Abstract

Background. *Deeper understanding on the risk factors and seeking potential predicted biomarkers for prognosis of total hip arthroplasty (THA) patients are of great significance. Limited researches focused the correlation between high mobility group box protein-1 (HMGB1) and the prognosis of THA patients.* **Objective.** *The objective of this study was to investigate the role of HMGB1 and inflammatory factors in patients underwent total hip arthroplasty (THA).* **Methods.** *The present prospective study enrolled 208 THA patients who went to our hospital during January 2020 to January 2022. Serum levels of HMGB1, C-reactive protein (CRP), interleukin-1β (IL-1β), and IL-6 were detected at the admission, 1 day, 3 days, 7 days, 30 days, and 90 days after surgery. The levels of Harris score, Fugl-Meyer, 36-item short-form health survey (SF-36), and Pittsburgh sleep quality index (PSQI) were detected on 90 days after surgery in two groups. Receiver operating characteristic curve (ROC) was performed for analyzing the diagnostic value of HMGB1 and logistic regression model was used for identifying the risk factor for poor prognosis of THA patients.* **Results.** *Serum levels of HMGB1 and inflammatory factors increased after surgery compared with the baselines. A positive correlation was found between HMGB1 and CRP on 1 day after surgery, and positive correlations were found among HMGB1, IL-1β, and IL-6 on 3 day after surgery. Besides, low HMGB1 reduced the incidence of post-operative complications and improved prognosis of THA patients.* **Conclusion.** *Serum HMGB1 was correlated with inflammatory factors and the prognosis of THA patients.*

Keywords: *Total hip arthroplasty. High mobility group box 1. Inflammatory factors. Prognosis.*

Resumen

Profundizar la comprensión de los factores de riesgo y buscar predecir biomarcadores potenciales para el pronóstico de pacientes con reemplazo total de cadera es de gran importancia. Los estudios limitados se han centrado en la correlación entre la nhigh mobility group box 1 protein (HMGB1) y el pronóstico en pacientes con artroplastia total de cadera. **Objetivo.** *Investigar el papel de la HMGB1 sérica y los factores inflamatorios en pacientes sometidos a artroplastia total de cadera.* **Método.** *Estudio prospectivo que incluyó 208 pacientes con artroplastia total de cadera que acudieron a nuestro hospital. Los niveles de puntuación de Harris, Fugl-Meyer, encuesta de salud de formato corto de 36 ítems (SF-36) e índice de calidad del sueño de Pittsburgh (PSQI) se determinaron 90 días después de la cirugía en dos grupos. Se realizó la curva característica operativa del receptor (ROC) para analizar el valor diagnóstico de HMGB1 y se utilizó un modelo de regresión logística para identificar*

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el factor de riesgo para mal pronóstico de los pacientes con artroplastia total de cadera. **Resultados.** *Las concentraciones séricas de HMGB1 y los factores inflamatorios aumentaron después de la cirugía en comparación con los valores iniciales. Se encontró una correlación positiva entre la HMGB1 y la proteína C reactiva 1 día después de la cirugía, y correlaciones positivas entre la HMGB1 y las interleucinas 1β y 6 a los 3 días de la cirugía.* **Conclusiones.** *La HMGB1 sérica se correlacionó con los factores inflamatorios y con el pronóstico de los pacientes con artroplastia total de cadera.*

***Palabras clave*:** *Artroplastia total de cadera. HMGB1. Factores inflamatorios. Pronóstico.*

Introduction

Total hip arthroplasty (THA) is one the most successfully orthopedic interventions for severe osteoarthritis[1]. The revolutionary treatment for hip arthritis shows an annual increase over 5.4% and an estimated increase of 200% in demand for THA by 2030[2]. Recently, three surgical approaches were commonly used in THA procedure, including the direct anterior, direct lateral and posterior approaches, with cost-effective treatment for pain relief, and function improvement in hip[3]. Although numerous studies confirm the effects of THA on joint diseases[4,5], the clinical outcomes and prognosis are still unsatisfied. Thus, deeper understanding on the risk factors and seeking potential predicted biomarkers for prognosis of THA patients are of great significance.

High mobility group box protein-1 (HMGB1) is a kind of nuclear proteins binding to DNA[6]. Recent evidence shows the pathogenic function of HMGB1 in inflammatory diseases. As reported, cellular activation, stress, damage, or necrosis induced the release of HMGB1, which, in turn, triggered inflammatory response in cells[7]. HMGB1 bound to Toll-like receptors (TLRs) and the receptor for advanced glycation end products (RAGE) to activate inflammation in chronic and acute liver diseases, such as hepatocellular carcinoma, hepatic ischemia/reperfusion injury, and nonalcoholic fatty liver disease[8]. Recent studies suggested that increased HMGB1 was involved in the pathogenesis of arthritis. Monoclonal anti-HMGB1 partially alleviated joint destruction and obviously improved the clinical outcomes of mice with collagen type II-induced arthritis[9]. Elevated HMGB1 was found in inflammatory synovial tissue of RA patients and collagen-induced arthritis rats; besides, HMGB1 expression was positively correlated with TNF-α and interleukin-1β (IL-1β) at the peak[10]. Another study also illustrated that the progression of arthritis was accelerated by overexpressed HMGB1 but inhibited by reduced HMGB1, suggesting HMGB1 was a mediator for inflammation and a novel target for arthritis[11]. In addition, the close association between inflammatory factors and postoperative recovery and complications was also reported. Significantly positive relationships was observed between the peak levels of C-reactive protein (CRP) and IL-6 and complication rate after THA, suggesting inflammatory factors might be the predictors for the post-operative complications in patients underwent THA[12]. However, limited researches demonstrated the correlation between HMGB1 and inflammatory factors and the prognosis of THA patients.

In the present study, we demonstrated that increased HMGB1 and inflammatory factors were correlated with poor prognosis of THA patients, indicating the potential therapeutic role of HMGB1 and inflammatory factors for the clinic outcomes and prognosis of THA patients.

Methods

Patients

A total of 208 THA patients who were admitted in our hospital during January 2020 to January 2022 were included in this prospective observational study. The inclusion criteria were as follows: (1) All adult patients aged over 18 years diagnosed with secondary osteoarthritis including post-traumatic, osteonecrosis, or secondary to inflammatory arthropathy; (2) patients underwent primary THA; (3) no abnormality around the hip joint was found in the anatomy; and (4) patients without deep venous thrombosis when admission. The exclusion criteria were as follows: (1) serious pre-operative complications, such as malignant tumors, severe renal, liver, or cardiovascular diseases; (2) mental diseases; and (3) pathological hip fractures caused by tumor. This study was approved by the ethic committee of our hospital. Written informed consent was obtained from all patients.

THA surgery

All the patients received standardized operation conducted by operating surgeons as described

previously[13]. Three approaches were chosen for THA in all patients according to special conditions, including posterior approach, direct lateral approach, and anterior approach. A standardized intraoperative protocol and routine post-operative management protocol were obeyed, including the use of tranexamic acid and local infiltration anesthesia. A X-ray examination was performed at 6 weeks after surgery.

Detection of serum HMGB1 and inflammatory factors

Venous blood samples of 5 ML were collected from all patients at admission, 1 day, 3days d, 7 days, 30 days, and 90 days after surgery. The serum HMGB1 and inflammatory factors were determined using the following ELISA kits: HMGB1 ELISA kit (#MBS451177, 62.5-4000 pg/mL), IL-1β ELISA kit (#MBS175901, 3.9 -250 pg/mL), and IL-6 ELISA kit (#MBS2701078, 7.8–500 pg/mL). The serum level of CRP was detected using a Hitachi 7600 Automatic Biochemical Analyzer (Hitachi Corporation).

Clinical outcomes and follow-up

Demographic data including sex, BMI, pre-operative, and post-operative complications were collected from the database. The levels of Harris and Fugl-Meyer were detected on admission and 90 days after surgery in all patients, and the levels of 36-item short-form health survey (SF-36) and Pittsburgh sleep quality index (PSQI) were detected on 90 days after surgery in all patients. For patients with Harris Hip Score ≥ 80 were defined as good prognosis, the others with Harris Hip Score < 80 were defined as poor prognosis. All patients were followed up for 3 months.

Data analysis

The normally distributed data were expressed as mean ± SD. Comparison for continuous data were analyzed by Student t-test. The rates were analyzed by Chi-square test. Receiver operating characteristic curve (ROC) was used for assessing the diagnostic value of HMGB1 in patients with poor prognosis. In addition, the risk factors for poor prognosis of THA patients were analyzed by logistic regression model. All the calculation and graph were conducted using SPSS 18.0 and Graphpad Prism Software 6.0.

Table 1a. Correlation among HMGB1, CRP, IL-1β and IL-6 on 1 day after surgery in all patients

	HMGB1	CRP	IL-1β	IL-6
HMGB1				
Person's correlation	1	0.784	–0.053	0.001
p	-	< 0.001	0.444	0.994
CRP				
Person's correlation	0.784	1	–0.081	–0.031
p	< 0.001	-	0.243	0.661
IL-1β				
Person's correlation	–0.053	–0.081	1	0.020
p	0.444	0.243	-	0.779
IL-6				
Person's correlation	0.001	–0.031	0.020	1
p	0.994	0.661	0.779	-

HMGB1: high level of high mobility group box 1; CRP: C-reactive protein; IL-1β: interleukin-1β; IL-6: interleukin-6.

Results

Dynamic changes and the correlation of serum HMGB1 and inflammatory factors in all THA patients

Serum HMGB1 and inflammatory factors in all patients were detected at the admission, 1 day, 3 days, 7 days, 30 days, and 90 days after surgery (Fig. 1). Compared with the admission, serum levels of HMGB1, IL-1β, and IL-6 were obviously increased on 1 day and 3 days after surgery, and then gradually declined ($p < 0.05$). Serum CRP showed a peak value at 1 day after surgery and then gradually declined ($p < 0.05$). No significant difference was observed after 30 days after the surgery. In addition, the results showed significantly positive correlation between HMGB1 and CRP on 1 day after surgery ($p < 0.05$, Table 1a). Positive correlations were found among HMGB1, IL-1β, and IL-6 on 3 day after surgery ($p < 0.05$, Table 1b). Analysis showed no obvious correlations among HMGB1, IL-1β, IL-6, and CRP on 7 day after surgery ($p > 0.05$, Table 1c).

HMGB1 was correlated with post-operative complications and prognosis of THA patients

To further study the association between HMGB1 and prognosis of all THA patients, all the participants were divided into high HMGB1 group and low HMGB1 group according to the mean value of serum HMGB1 704.04 pg/

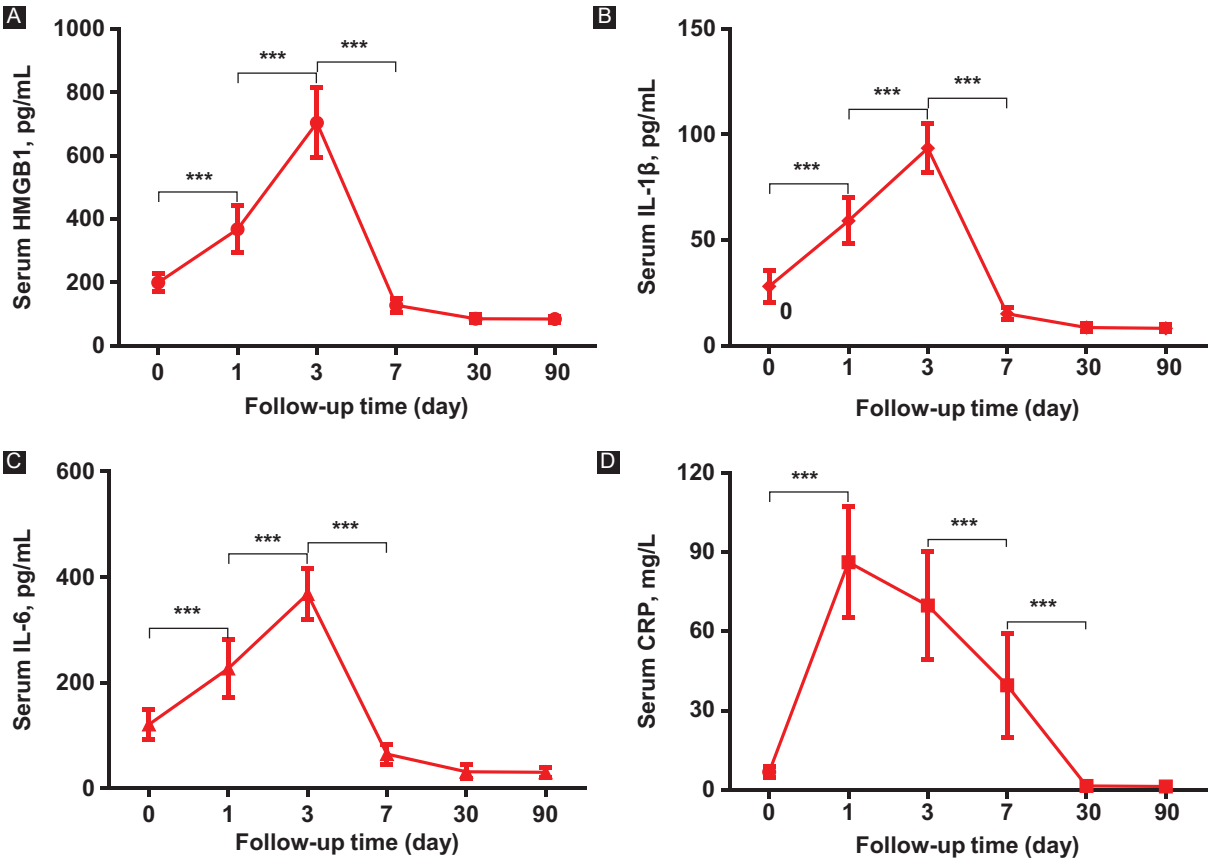

Figure 1. *Dynamic changes of serum high mobility group box 1 and inflammatory factors in all total hip arthroplasty (THA) patients.*

mL on 3 day after surgery. Table 2 showed basic clinical characteristics of all patients in two groups. Serum levels of CRP, IL-1β, and IL-6 were significantly higher in high HMGB1 group compared with low HMGB1 group on 3 days after surgery ($p < 0.05$). No significant difference was found for the other basic characteristics between two groups.

The association between serum HMGB1 and the prognosis of THA patients was also analyzed. The levels of Harris, Fugl-Meyer, SF-36, and PSQI were compared between high HMGB1 group and low HMGB1 group on 90 d after surgery. As shown in table 3, the levels of Harris, Fugl-Meyer, and SF-36 were in low HMGB1 group, which were significantly higher than those in high HMGB1 group ($p < 0.05$). The incidence of infection and deep venous thrombosis in high HMGB1 group was much higher than low HMGB1 group ($p < 0.05$). However, no significant difference was observed for PSQI and the incidence of nausea and vomiting in two groups. All these results indicated that low HMGB1 reduced the incidence of post-operative complications and improved prognosis of THA patients.

High level of HMGB1 predicted poor prognosis for THA patients

Finally, we analyzed the diagnostic value of HMGB1 for THA patients. For all THA patients, Harris Hip score < 80 was considered as poor prognosis and Harris score ≥ 80 was considered as good prognosis. ROC curve was used to investigate the diagnostic value of HMGB1 on 3 days after surgery. The data showed that the cutoff value of HMGB1 for poor prognosis was 806.45 pg/mL, with AUC 0.926 (95% CI 0.876~0.975), sensitivity 87.50%, and specificity 82.8% (Fig. 2). Logistic regression model suggested that HMGB1 was the risk factor for poor prognosis of THA patients (odd ratio > 1, $p < 0.05$, Table 4). These findings illustrated that serum HMGB1 exhibited valuable diagnostic potential for poor prognosis of THA patients; besides, HMGB1 was also the risk factors for poor prognosis in THA patients.

Table 1b. Correlation among HMGB1, CRP, IL-1β and IL-6 on 3 days after surgery in all patients

	HMGB1	CRP	IL-1β	IL-6
HMGB1				
Person's correlation	1	0.084	0.764	0.788
p	-	0.226	< 0.001	< 0.001
CRP				
Person's correlation	0.084	1	0.059	0.100
p	0.226	-	0.399	0.152
IL-1β				
Person's correlation	0.764	0.059	1	0.609
p	< 0.001	0.399	-	< 0.001
IL-6				
Person's correlation	0.788	0.100	0.609	1
p	< 0.001	0.152	< 0.001	-

HMGB1: high level of high mobility group box 1; CRP: C-reactive protein; IL-1β: interleukin-1β; IL-6: interleukin-6..

Table 1c. Correlation among HMGB1, CRP, IL-1β and IL-6 on 7 days after surgery in all patients

	HMGB1	CRP	IL-1β	IL-6
HMGB1				
Person's correlation	1	0.051	0.024	0.030
p	-	0.446	0.731	0.668
CRP				
Person's correlation	0.051	1	0.027	–0.029
p	0.446	-	0.695	0.673
IL-1β			1	0.007
Person's correlation	0.024	0.027	-	0.923
p	0.731	0.695		
IL-6				
Person's correlation	0.030	–0.029	0.007	1
p	0.668	0.673	0.923	-

HMGB1: high level of high mobility group box 1; CRP: C-reactive protein; IL-1β: interleukin-1β; IL-6: interleukin-6.

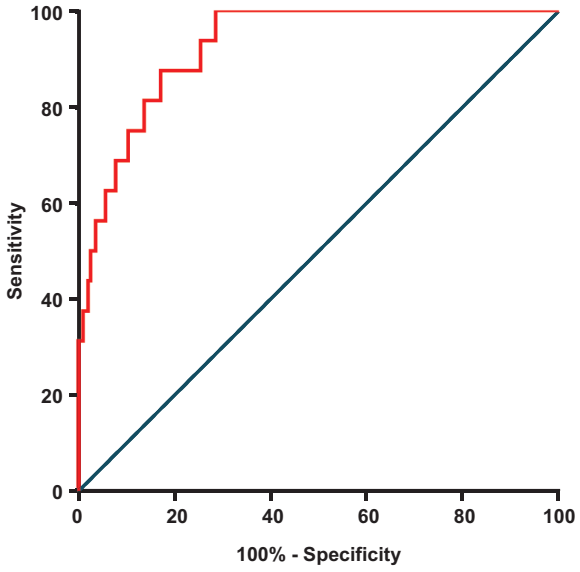

Figure 2. *High level of high mobility group box 1 (HMGB1) predicted poor prognosis for total hip arthroplasty (THA) patients. Receiver operating characteristic curve analysis of the diagnostic value of serum HMGB1 for poor prognosis of patients after THA surgery.*

Discussion

THA has been one of the major orthopedic operations widely performed in clinic practice[14]. THA is an ideal method for treating hip diseases, such as femoral neck fracture, femoral head necrosis, hip dysplasia, and so on[15]. Although THA significant improves the life quality of patients with hip diseases, the prognosis is not satisfied. Thus, new diagnostic biomarkers to predict the prognosis of THA patients are very essential. In the present research, we demonstrated that high level of HMGB1 and inflammatory factors was associated with poor prognosis in THA patients.

HMGB1 has been proven to be associated with the pathological mechanism and prognosis of patients with joint diseases. As reported, HMGB1 gene expression was increased in the articular cartilage in the mouse model of ischemic osteonecrosis and elevated HMGB1 activated IL-6 expression in the supernatants of chondrocytes, suggesting HMGB1 expression was significantly involved in the pathogenesis of Legg-Calvé-Perthes disease[16]. Upregulatd serum HMGB1 was found in ankylosing spondylitis patients; besides, serum HMGB1 could be identified as laboratory indicator to reflect the activity of ankylosing spondylitis[17]. HMGB1 inhibitors exhibited protective effect on osteoarthritis through suppressing IL-1β-induced MMPs expression through TLR4/NF-κB pathway in human articular chondrocytes-knee[18]. Suppression of BRD4 alleviated inflammatory response and catabolism of chondrocytes and inhibited the activation NF-κB pathway through recruiting HMGB1 in in articular cartilage of osteoarthritis[19]. Increasing number of evidence demonstrate the pathogenic features of HMGB1 in various diseases, suggesting the potential of HMGB1 as a new therapeutic option for rheumatoid arthritis[20] and osteoarthritis[21]. Nevertheless, the association between HMGB1 and the prognosis of patients received THA surgery is still uncertain. Our study for the 1st time investigated the role of HMGB1 in disease progression

Table 2. Clinical characteristics of all THA patients in two groups

Characteristics	High HMGB1 group (n = 108)	Low HMGB1 group (n = 100)	p value
Age, year	62.35 ± 11.18	63.66 ± 10.53	0.383
Female, n (%)	78 (72.22)	69 (69.00)	0.610
BMI, kg/m^2	25.93 ± 3.96	26.58 ± 5.23	0.314
Pre-operative complications, n (%)			
Diabetes	15 (13.89)	11 (11.00)	0.529
Hypertension	16 (14.81)	16 (16.00)	0.813
Pre-operative Harris score	34.89 ± 8.79	36.07 ± 10.72	0.388
Pre-operative Fugl-Meyer score	14.92 ± 2.99	14.13 ± 3.80	0.101
CRP on 3 days after surgery, mg/L	73.22 ± 19.76	66.29 ± 20.57	< 0001
IL-1β on 3 days after surgery, pg/mL	100.72 ± 8.76	85.59 ± 8.43	< 0001
IL-6 on 3 days after surgery, pg/mL	400.04 ± 37.02	334.22 ± 33.12	0.014
Approaches for THA, n (%)			
Posterolateral approach	60 (55.56)	59 (59.00)	0.616
Direct anterior approach	48 (44.44)	41 (41.00)	

HMGB1: high level of high mobility group box 1; CRP: C-reactive protein; IL-1β: interleukin-1β; IL-6: interleukin-6; THA: Total hip arthroplasty; BMI: body mass index.

Table 3. Comparison of post-operative complications and prognosis in two groups

Variables	High HMGB1 group (n = 108)	Low HMGB1 group (n = 100)	p value
Harris on 90 days	86.37 ± 6.65	89.72 ± 6.02	< 0.001
Fugl-Meyer on 90 days	23.85 ± 2.64	27.64 ± 4.23	< 0.001
SF-36 on 90 days	74.56 ± 9.42	83.62 ± 7.22	< 0.001
PSQI on 90 days	8.26 ± 4.45	7.69 ± 4.23	0.346
Post-operative complications, n (%)			
Nausea and vomiting	12 (11.11)	12 (12.00)	0.841
Infection	11 (10.19)	2 (2.00)	0.020
Deep venous thrombosis	27 (25.00)	4 (4.00)	< 0.001
Dislocation rates	2 (1.85)	1 (1.00)	-
Length of stay	9.22 ± 2.01	8.84 ± 1.75	0.146

HMGB1: high level of high mobility group box 1; PSQI: Pittsburgh sleep quality index.

Table 4. Logistic regression analysis for risk factors for poor prognosis

Variables	B	SE	Wald	Sig.	OR (95%CI)
HMGB1 on 3 days	0.020	0.010	4.130	0.042	1.020 (1.001~1.040)
IL-1β on 3 days	0.004	0.046	0.006	0.936	1.004 (0.918~1.097)
IL-6 on 3 days	0.021	0.016	1.590	0.207	1.021 (0.989~1.054)
CRP on 3 days	–0.023	0.020	1.320	0.251	0.978 (0.941~1.016)

HMGB1: high level of high mobility group box 1; CRP: C-reactive protein; IL-1β: interleukin-1β; IL-6: interleukin-6; SE: standard error; OR: odds ratio; CI: confidence interval.

and its correlation with the clinic outcomes of THA patients. Our data showed that lower HMGB1 reduced the incidence of post-operative complications and improved prognosis of THA patients. In addition, serum HMGB1 was a diagnostic biomarker and risk factor for poor prognosis of THA patients.

Recent data showed the relationship between inflammation and HMGB1 reported in joint diseases. A prospective study revealed obvious elevation of serum HMGB1 and white blood cells (WBC) in patients with prosthetic joint infection, suggesting a underlying correlation between HMGB1 and WBC in joint infection[22]. As a mediator of inflammation in rheumatoid arthritis, HMGB1 level increased with proinflammatory S100 protein and IL-8 in synovial fluid collected from patients diagnosed with the early onset juvenile idiopathic arthritis[23]. A previous study illustrated that cytoplasmic and extracellular HMGB1 expression elevated

along with the development of collagen-induced arthritis; additionally, cytoplasmic HMGB1 expression was consistent with the level of TNF-α and IL-1β in advanced arthritis[24]. HMGB1 was reported to sustain chronic synovitis through several mechanisms including the upregulation of IL-1, IL-6, and TNF-α; however, extensive production of proinflammatory cytokines mediated tissue damage. Besides, a significantly correlation was found between serum HMGB1 and IL-6 in postmenopausal women with rheumatoid arthritis[25]. Consistent with previous studies, our findings revealed positive correlation between HMGB1 and IL-1β on 3 day after surgery, and positive correlation between HMGB1 and CRP was found on 1 day after surgery. The involvement of inflammatory factors in joint diseases was also reported in various studies. IL-1β aggravated the production of osteoclastogenic Tregs, resulting in the bone erosion in arthritis[26]. The increase of IL-6 and sIL-6R might increase the risk of joint destruction through upregulating VEGF expression in rheumatoid arthritis patients[27]. Our study also identified HMGB1, IL-1β, and IL-6 as the risk factors for poor prognosis in THA patients.

Conclusion

In summary, the present study found that the contents of HMGB1 and inflammatory factors were decreased after THA surgery and positive correlations were found between HMGB1 and inflammatory factors in patients. Besides, high level of HMGB1 increased the complication rates and predicted poor prognosis for patients with THA surgery. Our results might provide new insights for the role of HMGB1 and inflammatory factors in THA patients.

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Conflicts of interest

The authors declare no potential conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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