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ORIGINAL ARTICLE

Predictive value of bone morphogenetic protein-7, thromboxane A2, and osteoprotegerin for prognosis of patients with distal radius fractures

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ABSTRACT

Objectives: This study aims to investigate the predictive value of bone morphogenetic protein-7 (BMP-7), thromboxane A2 (TXA2), and osteoprotegerin (OPG) for the prognosis of patients with distal radius fractures.

Patients and methods: Between January 2021 and January 2022, a total of 124 patients (71 males, 53 females; mean age: 49.8±5.1 years; range, 34 to 68 years) with distal radius fractures were included in the fracture group. Healthy volunteers receiving physical examination in our hospital in the same period were included in the control group (n=50; 29 males, 21 females; mean age: 50.1±5.4 years; range, 35 to 68 years). The expressions of BMP-7, TXA2, and OPG in the peripheral blood were detected. In the fracture group, 124 patients underwent internal fixation after inclusion and followed for six months. The prognosis was evaluated based on the Gartland & Werley scoring system for wrist joint function. The factors influencing prognosis were analyzed, and the predictive values of BMP-7, TXA2, and OPG were calculated.

Results: Age, fracture classification, early loss of palmar tilt, late loss of palmar tilt, time to return to exercise after surgery, BMP-7, TXA2, and OPG were all factors influencing the prognosis ($p<0.05$). For predicting the prognosis, the area under the ROC curve of BMP-7 + TXA2 + OPG (0.928) was significantly larger than those of BMP-7 (0.810), TXA2 (0.856) and OPG (0.823) alone, and BMP-7 + TXA2 + OPG had the highest predictive efficiency. The BMP-7 was negatively correlated with TXA2 (r=-0.471), but positively correlated with OPG (r=0.437).

Conclusion: The combined detection of BMP-7, OPG, and TXA2 is highly valuable for predicting the prognosis of patients with distal radius fractures.

Keywords: Bone morphogenetic protein-7; distal radius fracture; osteoprotegerin; tromboksan A2.

Distal radius fractures are a common type of clinical fractures arising within 3 cm of the articular surface of the distal radius. Such fractures would inevitably affect the wrist function of patients, and bring some adverse effects on the quality of life of the patients. The prognosis of patients with good joint function recovery is crucial for improving the quality of life of patients.[1] Belonging to the transforming growth factor-alpha (TGF-β) family, bone morphogenetic protein-7 (BMP-7) has been verified to promote the rapid recovery of bone injuries in clinic.[2] Thromboxane A2 (TXA2) is a vasoactive factor. Its content rises sharply after the development of fractures, and declines during fracture healing, showing a positive correlation with the severity of fracture.[3] Osteoprotegerin (OPG), known as an osteoclast inhibitor, is lowly expressed at the early stage of fractures, but its content is elevated in the process of fracture healing.[4]

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In the present study, we aimed to investigate the value of the combined detection of BMP-7, TXA2, and OPG in predicting the prognosis of patients with distal radius fractures and to examine the correlations of the levels of these indicators with the prognosis to provide a reference for early prognostic evaluation.

PATIENTS AND METHODS

This is a single-center, prospective study was conducted at Trauma Center, The First People's Hospital of Lianyungang Department of Emergency Surgery between January 2021 and January 2022. A total of 124 patients (71 males, 53 females; mean age: 49.8±5.1 years; range, 34 to 68 years) with distal radius fractures treated in our hospital were included in the fracture group. Healthy volunteers receiving physical examination in our hospital in the same period were included in the control group (n=50; 29 males, 21 females; mean age: 50.1±5.4 years; range, 35 to 68 years). Inclusion criteria were as follows: In the fracture group, having a diagnosis of distal radius fractures based on clinical and imaging examinations and complicated with no nerve and blood vessel injuries. In the control group, healthy volunteers with normal indicators in all examinations, indicating no disease, were included. Exclusion criteria were as follows: age <18 years, patients with open fractures, multiple fractures or pathological fractures, those with major organ dysfunction, those with malignant tumors, those with abnormal coagulation function, those with mental illness, or those unable to communicate. Demographic and clinical data of all participants were recorded.

Detection methods of BMP-7, TXA2, and OPG

The fracture group was admitted to our hospital within 2 h after fractures, and 5 mL of venous blood was collected immediately after inclusion. Meanwhile, 5 mL of venous blood was collected from each participant of the healthy group immediately after inclusion. Then, the blood samples were centrifuged for 15 min (r=5 cm, 3,000 rpm) after natural agglutination. Later, the upper serum obtained was stored at -80°C after subpackaging for subsequent research.

Detection of BMP-7: The expression of BMP-7 was measured by real-time fluorescence quantitative polymerase chain reaction (RT-qPCR). Specifically, the total ribonucleic acid (RNA) was extracted from serum, reversely transcribed into the complementary deoxyribonucleic acid (cDNA) on the reaction system prepared according to the instructions of Reverse Aid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Waltham, MA, USA), and amplified using 2×SYBR Green qPCR Master Mix (Thermo Fisher Scientific, Waltham, MA, USA). The conditions for PCR included pre-denaturation at 95°C for 5 min, followed by 38 cycles of denaturation at 94°C for 30 sec, annealing at 54°C for 45 sec and extension at 72°C for 5 min, and extension at 72°C for 5 min. Finally, the expression of BMP-7 was calculated by 2-ΔΔCt method, and β-Actin was taken as an internal reference. Primers used included: BMP-7-Forward: 5'-TGGAAAGATCAAACCGGAAC-3' and BMP-7-Reverse: 5'-CAGCCTGCAAGATAGCCATT-3', and β-Actin-Forward: 5'-GCGAGAAGATGACCCACCACC-3', and β-Actin-Reverse: 5'-ATGTCACGCACGATTTCCTATTA-3'.

Detection of TXA2 and OPG: Enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of TXA2 and OPG in the prepared serum using a fully-automatic multifunctional microplate (SL-3506, YLINST).

Treatment methods

The therapeutic methods for patients with distal radius fractures were selected according to their fractures and physical conditions. Patients with operative indications such as unstable fracture, radius shortening >3 mm after manual reduction, dorsal angulation >10°, and intra-articular fracture with obvious displacement or step >2 mm were treated with open reduction plus locking plate internal fixation, while those without the aforementioned operative indications received conservative treatment. The patients underwent comprehensive evaluation before operation and actively completed various examinations. For patients aged ≥60 years, their past history was inquired in detail, and brain and lung computed tomography (CT), echocardiography, and related cardiac indicator tests were additionally performed. In case of abnormal test and examination results, consultation by relevant departments was required to correct related indicators of the patients and assess the operation risk. Finally, 12 out of the 124 patients received conservative treatment, 50 patients were treated with open reduction plus locking plate internal fixation via the dorsal approach, and 62 patients were provided with open reduction plus locking plate internal fixation via the palmar approach. All the operations were accomplished by a single team of surgeons. Manual reduction plus cast stabilization was adopted for patients receiving conservative treatment.

In terms of open reduction plus locking plate internal fixation via the palmar approach, the patients were placed in the supine position after general

anesthesia, with the affected limb abducted and the forearm fully supinated on the operation table. Then, an incision was made on the distal forearm, and an access was established from the flexor carpi radialis and inter-muscular branch of radial artery. Next, the flexor carpi radialis was pulled to the ulnar side, and the radial artery was pulled to the radial side to expose the pronator quadratus muscle. Subsequently, the part of the muscle was stripped off to expose the fractured end. The incision was enlarged beyond the transverse wrist crease, and the part of the transverse carpal ligament was severed, pulled longitudinally, pried and repositioned, so as to restore the length of the distal radius and the smoothness of the fracture surface as much as possible and recover the normal anatomical positions of the volar tilt angle, ulnar inclination angle, and distal radioulnar joint. Afterward, a contoured T-shaped steel plate was placed on the palmar surface of the distal radius, and fixed on the radius through lag screws. After satisfying fracture reduction and articular surface were confirmed by fluoroscopy, the locking screws were fixed sequentially from the ulnar side to the radial side and from the distal end to the proximal end. Later, the skin flap was pulled to the radial side to expose the styloid process of radius, the curved steel plate was attached to the dorsal side of the radius, the locking screws were inserted, and fluoroscopy was conducted again to confirm that no screw entered the joint cavity. The wrist joint was moved passively to check the stability of the fixation and exclude the possibility of screws entering the joint space accidentally. After confirmation of no abnormalities, the pronator quadratus muscle was repaired, and the incision was sutured layer by layer.

As for the open reduction plus locking plate internal fixation via the dorsal approach, the patients chose the distal dorsal approach from the distal radius, approximately 80 mm from the Lister nodule in the dorsal wrist to the proximal end. After pulling radially to an appropriate position, the part of the joint capsule was incised to fully expose the dorsal articular surface of radius and the fractured end. Subsequently, the bone fragments on the palmar side were probed, fracture reduction was carried out, and the incision was cleaned and disinfected. Finally, the incision was sutured layer by layer.

Follow-up of prognosis

In the fracture group, 124 patients underwent internal fixation after inclusion, after which they were followed for six months. Based on the Gartland & Werley scoring system for wrist joint function,[5] the prognosis of patients was evaluated, involving residual deformity, subjective evaluation, objective evaluation and complications. According to the final score, the prognosis was evaluated as excellent (0-2 points), good (2-8 points), fair (9-20 points) and poor (≥21 points) and, accordingly, the patients were divided into good-to-excellent group and poor-to-fair group.

Collection of overall data of patients

The following overall data of patients were collected, including sex (male/female), age (≥60/<60 years), cause of injury (fall on the ground/traffic accident/fall from a high place), affected side (dominant side/non-dominant side), fracture classification (type A/type B/type C), smoking and drinking history (Yes/No), complication with internal medical diseases (Yes/No), early loss of palmar tilt (>10°/<10°), late loss of palmar tilt (>10°/<10°), time from injury to surgery (≥7 or <7 days), surgical approach (conservative treatment/pars dorsalis/palmaris), and time to return to exercise after surgery (≥14 or <14 days).

Observational indicators

The expressions of BMP-7, TXA2 and OPG were compared between the fracture group and healthy group. Besides, the overall data collected from patients and the expressions of BMP-7, TXA2, and OPG were compared between good-to-excellent group and poor-to-fair group. Then, the factors that influence the prognosis of patients with distal radius fractures were analyzed, and receiver operating characteristic (ROC) curves were plotted to assess the value of BMP-7, TXA2 and OPG in predicting the prognosis of patients with distal radius fractures. Finally, the Pearson correlation analysis was used to investigate the correlations among BMP-7, TXA2, and OPG.

Statistical analysis

The sample size was calculated according to the equation of two-sample comparison test $n=[P1(1-P1)+P2(1-P2)]/(P2-P1)2\times F(\alpha\cdot\beta)$, where the test level α is 0.05 and the power (1-β) is 90%. According to the equation, 110 cases should be included in each group. However, considering the dropout rate, the sample size was enlarged to 124 cases for each group based on the inclusion and exclusion criteria. As to the healthy group, 50 cases were included due to the small number of subjects receiving physical examination in our hospital in the same period.

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Whether the data conformed to normal distribution was determined by the

TABLE I
Expressions of BMP-7, TXA2, and OPG in fracture and healthy groups

Groups	n	BMP-7	TXA2 (ng/L)	OPG (ng/L)
Fracture group	124	0.45±0.09	345.21±48.92	90.82±10.23
Healthy group	50	1.34±0.21	204.82±23.61	169.92±15.64
t		39.210	19.380	39.280
p		<0.001	<0.001	<0.001

BMP-7: Bone morphogenetic protein-7; TXA2: Thromboxane A2; OPG: Osteoprotegerin.

TABLE II
Overall data of patients in good-to-excellent and poor-to-fair groups

	Good-to-excellent group (n=101)		Poor-to-fair group (n=23)			
	n	%	n	%	Statistical value	*p*
Age (year)						
≥60	32	31.68	15	65.22	8.951	0.003
<60	69	68.32	8	34.78		
Sex						
Male	58	57.43	13	56.52	0.006	0.937
Female	43	42.57	10	43.48		
Cause of injury						
Fall on the ground	33	32.67	9	39.13		
Traffic accident	41	40.59	7	30.43	0.824	0.662
Fall from a high place	27	26.73	7	30.43		
Affected side						
Dominant side	56	55.45	13	56.52	0.009	0.925
Non-dominant side	45	44.55	10	43.48		
Fracture classification						
Type A	47	46.53	3	13.04		
Type B	34	33.66	5	21.74	19.750	<0.001
Type C	20	19.80	15	65.22		
Smoking and drinking history						
Yes	34	33.66	8	34.78	0.010	0.918
No	67	66.34	15	65.22		
Complication with internal medical diseases						
Yes	22	21.78	4	17.39	0.218	0.641
No	79	78.22	19	82.61		
Early loss of palmar tilt						
>10°	43	42.57	20	86.96	14.765	<0.001
<10°	58	57.43	3	13.04		
Late loss of palmar tilt						
>10°	32	31.68	21	91.30	27.211	<0.001
<10°	69	38.61	2	8.70		
Time from injury to surgery (day)						
≥7	52	51.49	13	56.52	0.191	0.662
<7	49	48.51	10	43.48		
Surgical approach						
Conservative treatment	10	9.90	2	8.70		
Pars dorsalis	40	39.60	10	43.48	0.125	0.940
Palmaris	51	50.50	11	47.83		
Time to return to exercise after surgery (day)						
≥14	38	37.62	19	82.61	15.264	<0.001
<14	63	62.38	4	17.39		

Kolmogorov-Smirnov test. Descriptive data were expressed in mean ± standard deviation, median (min-max) or number and frequency, where applicable. Normally distributed variables were compared between two groups using the independent samples t-test, while the measurement data not conforming to normal distribution were subjected to natural logarithmic transformation and analyzed with the non-parametric test. Categorical data were analyzed using the chi-square test. Logistic regression analysis was used to assess the factors influencing the prognosis. The ROC curve was plotted to analyze the value of BMP-7, TXA2 and OPG for predicting the prognosis. The Pearson correlation analysis was carried out to analyze the correlations among BMP-7, TXA2 and OPG. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline data of the participants were comparable between the groups.

Expressions of BMP-7, TXA2, and OPG in fracture and healthy groups

The fracture group had lower expressions of BMP-7 and OPG, but a higher expression of TXA2 than the healthy group (p<0.05) (Table I).

Overall data of patients in good-to-excellent and poor-to-fair groups

No statistically significant differences were observed in sex, cause of injury, affected side, smoking and drinking history, complication with internal medical diseases, surgical approach, and time from injury to surgery between good-to-excellent group and poor-to-fair group (p>0.05). However, the poor-to-fair group had significantly more patients aged ≥60 years, with type C fracture, early loss of palmar tilt of >10°, late loss of palmar tilt of >10°, and time to return to exercise after surgery of ≥14 days than those of the good-to-excellent group (p<0.05) (Table II).

Expressions of BMP-7, TXA2, and OPG and prognostic scores of good-to-excellent and poor-to-fair groups

Compared to the good-to-excellent group, the expressions of BMP-7 and OPG were lower and the expression of TXA2 was higher in the poor-to-fair group (p<0.05). The prognostic score of the poor-to-fair group was significantly higher than that of the good-to-excellent group (p<0.05) (Table III).

Correlations of expressions of BMP-7, TXA2, and OPG with prognostic scores

The correlation analysis showed that BMP-7 and OPG levels were negatively correlated with the prognosis scores of patients with distal radius fractures (r=-0.462, r=-0.411, p<0.05), whereas TXA2 level was positively correlated with the score (r=0.546, p<0.05) (Table IV).

Factors influencing prognosis of patients with distal radius fractures

Logistic regression analysis was performed with variables showing differences between good-to-excellent group and poor-to-fair group in

TABLE III
Expressions of BMP-7, TXA2, and OPG and prognostic scores of good-to-excellent and poor-to-fair groups

Groups	Case number	BMP-7	TXA2 (ng/L)	OPG (ng/L)	Prognostic score (point)
Good-to-excellent	101	0.79±0.11	302.81±42.51	135.49±20.07	4.53±0.68
Poor-to-fair	23	0.20±0.08	387.92±57.83	67.82±9.81	20.98±2.32
t		24.270	8.069	15.710	91.932
p		<0.001	<0.001	<0.001	<0.001

BMP-7: Bone morphogenetic protein-7; TXA2: Thromboxane A2; OPG: Osteoprotegerin.

TABLE IV
Correlations of expressions of BMP-7, TXA2, and OPG with prognostic scores

	BMP-7		TXA2		OPG	
	r	*p*	r	*p*	r	*p*
Prognostic score	-0.462	<0.001	-0.411	<0.001	0.546	<0.001

BMP-7: Bone morphogenetic protein-7; TXA2: Thromboxane A2; OPG: Osteoprotegerin.

TABLE V
Assignments of variable

Variables		Assignment
Dependent variable	Prognosis of patients with distal radius fracture	Excellent = 0, poor = 1
Independent variable	Age	<60 years old = 0, ≥60 years old = 1
	Fracture classification	Type A = 0, Type B = 1, Type C = 2
	Early loss of palmar tilt	<10° = 0, >10° = 1
	Late loss of palmar tilt	<10° = 0, >10° = 1
	Time to return to exercise after surgery	<14 day = 0, ≥14 day = 1
	BMP-7	Input original value
	TXA2	Input original value
	OPG	Input original value

BMP-7: Bone morphogenetic protein-7; TXA2: Thromboxane A2; OPG: Osteoprotegerin.

TABLE VI
Results of factors influencing prognosis of patients with distal radius fractures

	Regression coefficient	Standard error	Standardized regression coefficient	Wald value	*p*
Constant term	10.976	3.036	-	3.616	0.000
Age (reference: <60 years)					
≥60 years	3.592	1.226	0.178	2.561	0.005
Fracture classification (reference: type A)					
Type B	0.673	0.879	0.224	0.796	0.765
Type C	3.067	2.281	0.137	2.586	0.015
Early loss of palmar tilt (reference: <10°)					
>10°	4.213	1.897	0.209	2.417	0.018
Late loss of palmar tilt (reference: <10°)					
>10°	3.896	1.683	0.210	2.341	0.012
Time to return to exercise after surgery (reference: <14 day)					
≥14 day	-2.121	1.089	-0.125	-2.168	0.020
BMP-7	2.341	1.443	0.147	2.356	0.019
TXA2	3.421	1.067	0.156	2.679	0.000
OPG	2.497	1.329	0.118	2.887	0.000

BMP-7: Bone morphogenetic protein-7; TXA2: Thromboxane A2; OPG: Osteoprotegerin.

TABLE VII
Efficiency of BMP-7, TXA2, and OPG for predicting prognosis of patients with distal radius fractures

	AUC	95% CI	*p*	Sensitivity (%)	Specificity (%)	Youden index	Cut-off value
BMP-7	0.810	0.723~0.876	<0.001	83.32	77.86	0.720	0.92
TXA2	0.856	0.738~0.910	<0.001	87.84	76.12	0.767	300.21 ng/L
OPG	0.823	0.715~0.889	<0.001	85.61	75.42	0.734	129.92 ng/L
BMP-7+TXA2+OPG	0.928	0.812~0.987	<0.001	90.19	74.50	0.791	-

AUC: Area under the curve; CI: Confidence interval; BMP-7: Bone morphogenetic protein-7; TXA2: Thromboxane A2; OPG: Osteoprotegerin.

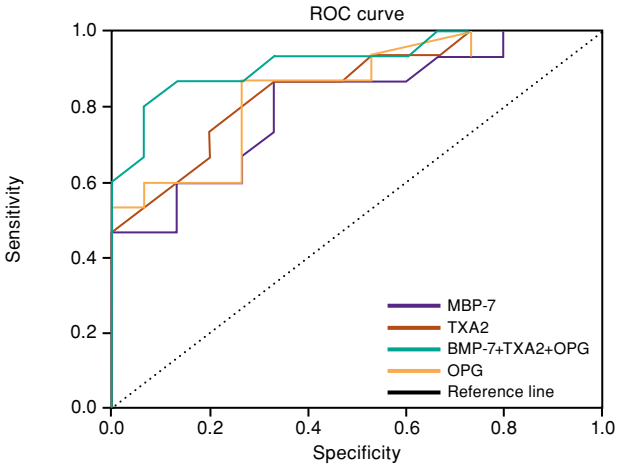


FIGURE 1. ROC curves of BMP-7, TXA2, and OPG in predicting prognosis of patients with distal radius fractures.
ROC: Area under curve; BMP-7: Bone morphogenetic protein-7; TXA2: Thromboxane A2; OPG: Osteoprotegerin.

Tables II and III as independent variables and the prognosis of patients with distal radius fractures as a dependent variable. The assignments of factors are shown in Table V. It was revealed that age of ≥60 years, type C fracture, early loss of palmar tilt of >10°, late loss of palmar tilt of >10°, time to return to exercise after surgery of ≥14 days, BMP-7, TXA2, and OPG were the factors influencing the prognosis of patients with distal radius fractures ($p<0.05$) (Table VI).

Value of BMP-7, TXA2, and OPG for predicting prognosis of patients with distal radius fractures

As illustrated by the ROC curves, in predicting the prognosis of patients with distal radius fractures, the area under curve (AUC) of BMP-7 + TXA2 + OPG (0.928) was significantly higher than that of BMP-7 (0.810), TXA2 (0.856) and OPG (0.823) alone, indicating that BMP-7 + TXA2 + OPG had the optimal predictive efficiency (Table VII and Figure 1).

Analysis results of correlations among BMP-7, TXA2, and OPG

The correlation analysis revealed that BMP-7 was negatively correlated with TXA2 ($r=-0.471$, $p<0.001$), but positively correlated with OPG ($r=0.437$, $p<0.001$), and TXA2 showed a negative correlation with OPG ($r=-0.557$, $p<0.001$) (Figure 2).

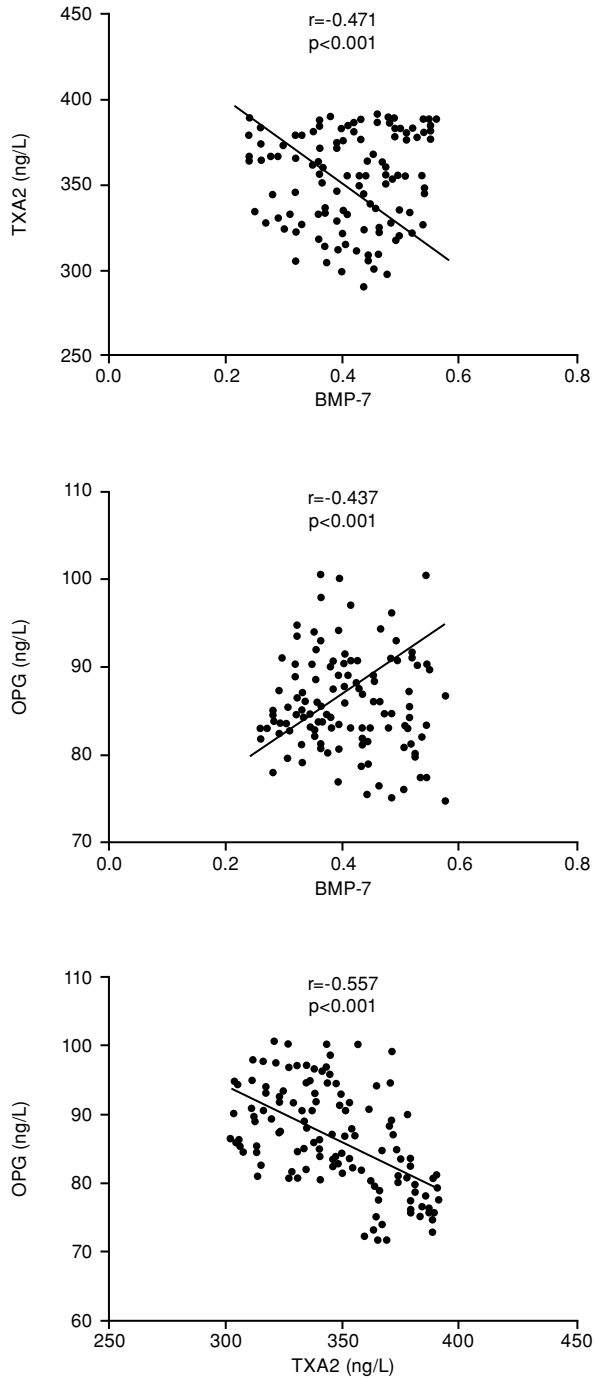


FIGURE 2. Analysis of correlations among BMP-7, TXA2, and OPG.
BMP-7: Bone morphogenetic protein-7; TXA2: Thromboxane A2; OPG: Osteoprotegerin.

DISCUSSION

Distal radius fractures are common fractures arising in the upper extremity in clinical practice. According to previous reports, such fractures mostly occur in individuals aged >50 years, primarily due to falling on the ground. To date, internal fixation has been the primary treatment for patients with distal radius fractures, yielding satisfactory efficacy.[6,7] However, it has been shown that, although the cure rate of distal radius fractures treated by internal fixation

is high, some patients still have poor prognosis and functional recovery, which poses threats to their daily life and work.[8] Therefore, it is essential to predict the prognosis of such patients at the early stage. Fracture-related cytokines have often been used to predict the prognosis and recovery of patients in the early stage. In this study, to avoid the influence of oxidative stress, blood samples were collected within 2 h after fractures to analyze the predictive values of BMP-7, TXA2, and OPG levels for the prognosis of patients with distal radius fractures. The combined detection of BMP-7, TXA2 and OPG was highly valuable in predicting the prognosis, indicating that the combined detection is beneficial to the early evaluation of patients' prognosis and functional recovery. In addition, targeted interventions can be performed as soon as possible for patients predicted with poor recovery in the early stage to improve their prognosis and quality of life.

Various cytokines experience dynamic changes during the functional recovery of various types of fractures after treatment.[9,10] The BMP-7 is a cytokine promoting fracture healing and injury repair. Some clinical studies have demonstrated that its expression decreases after the development of fractures, but its content gradually increases during fracture recovery to promote fracture healing. The BMP-7 regulates the transformation of bone mesenchymal hepatocytes into osteoblasts and accelerate the calcification of the cell matrix by facilitating the phosphorylation of osteoblasts, thereby suppressing the apoptosis of osteoblasts.[11] A study of Deng et al.[12] revealed that the increased level of BMP-7 in the BMP-7/Runx2 signaling pathway contributed to fracture healing. In the present study, we found that the expression of BMP-7 decreased after the development of fractures, suggesting that lowly expressed BMP-7 is unable to resist injuries after fractures occur. Similarly, Ali et al.[13] reported that BMP-7 was related to fractures. Furthermore, the relationship between BMP-7 and prognosis of the patient was analyzed, and the results showed that BMP-7 was correlated with the prognosis and functional recovery. In detail, the level of BMP-7 in patients with good-to-excellent prognosis was markedly higher than that in patients with poor-to-fair prognosis. This finding indicates that the BMP-7 expression is associated with the prognosis and recovery of patients with distal radius fractures, probably as BMP-7 is produced at the early stage of functional recovery after fracture healing, which facilitates the differentiation of primitive cells into osteoblasts to some extent, as well as the functional recovery of patients by inducing fracture healing.

The TXA2, a vasoactive factor, is regarded as a potent promotor for blood coagulation in clinic, and the content of TXA2 rises after trauma in the body.[14] According to previous studies,[15,16] the functional recovery after fracture surgery shows associations with the injured vascular endothelial cells and the microcirculation of the body. The TXA2 is a molecule regulating platelet aggregation, which plays a role in reducing the synthesis of cyclic adenosine monophosphate by decreasing the activity of adenylate cyclase, thereby facilitating platelet aggregation and thrombosis. The results of this study showed that those patients with distal radius fractures had a notably increased TXA2 content in peripheral blood compared to healthy individuals, implying that the patients with such fractures were in a hypercoagulable state where the TXA2 content was increased. Additionally, the TXA2 level decreased in patients with good-to-excellent prognosis, indicating a better functional recovery and decreased content of TXA2 in such patients with distal radius fractures.

Clinically, OPG is a secreted glycoprotein belonging to the tumor necrosis factor (TNF) receptor superfamily, which is primarily secreted by bone marrow mesenchymal stem cells and osteoblasts. Its expression can be detected in multiple tissues, including the gastrointestinal tract, lung, and heart tissues.[17,18] In a study, prostaglandin-E2, parathyroid hormone (PTH), interleukin-1, TNF-alpha (TNF-α), and other cytokines could regulate the expression of OPG, among which prostaglandin-E2 and PTH were inhibitors, while interleukin-1 and TNF-α were promotors for OPG expression.[19] In multiple diseases associated with bone injuries, including fractures, OPG can enhance the bone density of cortical bone and cancellous bone, suppress bone resorption, competitively and specifically bind receptor activator of nuclear factor kappa-B ligand (RANKL), and inhibit the differentiation of osteoclasts, thereby forming a RANK/RANKL/OPG system to promote bone healing and repair.[20,21] In the early stage of fracture, the activity of osteoclasts is higher than that of osteoblasts, and the secretion of OPG is insufficient. Over time, the activity of osteoclasts gradually decreases and the number of osteoblasts increases. At this time, through competitively binding RANKL, OPG inhibits the binding of RANKL to RANK, or binds RANKL/RANK to form a trimer, thereby suppressing osteolysis and promoting bone healing.[22] In this study, the OPG level of the fracture group was significantly lower than that of the healthy group, suggesting that, in the early stage of fracture, the activity of osteoclasts was higher than that of osteoblasts, and OPG secretion decreased to prevent

osteolysis. In this study, the fracture group showed an evidently lower OPG level than the healthy group, suggesting that OPG secretion is insufficient after the development of fractures. In addition, correlation analysis of OPG with the prognosis of patients demonstrated that the OPG level in good-to-excellent group was significantly higher than that in poor-to-fair group, indicating that enhanced secretion of OPG during fracture healing promotes bone healing and repair via its action on the RANK/RANKL/OPG system, ultimately facilitating the functional recovery of patients.

In this study, BMP-7, TXA2, and OPG, as independent risk factors for the prognosis of fracture patients, were linearly correlated. Probably, these factors interacted to promote bone healing. The combined detection of BMP-7, TXA2, and OPG had the highest predictive efficiency for the prognosis of patients with distal radius fractures, indicating that the prognosis of patients at the early stage can be predicted according to the expressions of the three factors to reduce the risk of poor prognosis.

Moreover, we found that age of ≥60 years and type C fracture were independent risk factors affecting the prognosis. Possibly, older patients had weaker body functions, slower fracture healing speed, and poorer willingness and compliance with functional exercise, which affected the recovery of joint function. With increasing fracture classification, the range and severity of joint involvement increased significantly, which thus increased the difficulty of surgery, prolonged the treatment and recovery time, and affected postoperative recovery. Therefore, for older patients, we should focus on their physical function, select an appropriate treatment method, and improve the compliance with functional exercise after treatment to accelerate the recovery. For patients with type C fractures, it is necessary to pay attention to radial shortening and articular surface collapse besides fracture fixation to avoid postoperative malunion. Based on the above factors, targeted measures can be formulated for early intervention, and early assessment can be conducted by monitoring serum BMP-7, TXA2, and OPG levels to avoid re-admission due to poor functional recovery and to reduce the economic burden.

Nonetheless, there are some limitations to this study. This is a single-center study with a small sample size and, therefore, the results may have been biased. In the future, multi-center, prospective studies with larger sample sizes are needed to confirm our study findings.

In conclusion, BMP-7 and OPG are lowly expressed and TXA2 is highly expressed in patients with distal radius fractures. The expressions of these three factors in patients with poor-to-fair prognosis are statistically significantly different from those in patients with good-to-excellent prognosis. Based on these findings, we suggest that the combined detection of expressions of BMP-7, OPG, and TXA2 has the highest predictive value for the prognosis of patients.

Ethics Committee Approval: The study protocol was approved by the The First People's Hospital of Lianyungang Ethics Committee (date: 04.01.2021, no: LW-20230522001-01). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Dağtaş MZ, Ünal ÖK. The external fixation can be a good alternative to plate-screw treatment in the surgical treatment of bilateral distal radius fractures: A retrospective cohort study. Jt Dis Relat Surg 2021;32:406-13. doi: 10.52312/jdrs.2021.151.
2. Xu X, Hui W, Liu N, Zhang Y. Effects of ergosteroside combined risedronate on fracture healing and BMP-2, BMP-7 and VEGF expression in rats. Acta Cir Bras 2021;36:e361107. doi: 10.1590/ACB361107.
3. Yin Y, Geng H, Cui S, Hua-Ji L. Correlation of platelet-derived growth factor and thromboxane A2 expression with platelet parameters and coagulation indices in chronic altitude sickness patients. Exp Physiol 2022;107:807-12. doi: 10.1113/EP089735.
4. Chaudhari SD, Sharma KK, Marchetto JJ, Hydren JR, Burton BM, Moreno AP. Modulating OPG and TGF-β1 mRNA expression via bioelectrical stimulation. Bone Rep 2021;15:101141. doi: 10.1016/j.bonr.2021.101141.
5. Gartland JJ, Jr, Werley CW. Evaluation of healed Colles' fractures. J Bone Joint Surg [Am] 1951;33:895-907.
6. Shapiro LM, Kamal RN; Management of Distal Radius Fractures Work Group. Distal radius fracture clinical practice guidelines-updates and clinical implications. J Hand Surg Am 2021;46:807-11. doi: 10.1016/j.jhsa.2021.07.014.

7. Bu G, Wei W, Li J, Yang T, Li M. Open reduction through original fracture line and fixation with locking plate is a feasible approach for extra-articular distal radius fracture malunion. Jt Dis Relat Surg 2022;33:489-95. doi: 10.52312/jdrs.2022.590.
8. Wang F, Zhang R, Liu S, Ruan H, Xu J, Kang Q. Severe spaghetti wrist injury: Should we expand the terminology from wrist to proximal forearm? Jt Dis Relat Surg 2022;33:273-84. doi: 10.52312/jdrs.2022.652.
9. Mathavan N, Raina DB, Tägil M, Isaksson H. Longitudinal in vivo monitoring of callus remodeling in BMP-7- and Zoledronate-treated fractures. J Orthop Res 2020;38:1905-13. doi: 10.1002/jor.24632.
10. Aluganti Narasimhulu C, Singla DK. The role of bone morphogenetic protein 7 (BMP-7) in inflammation in heart diseases. Cells 2020;9:280. doi: 10.3390/cells9020280.
11. Haubruck P, Tanner MC, Vlachopoulos W, Hagelskamp S, Miska M, Ober J, et al. Comparison of the clinical effectiveness of Bone Morphogenic Protein (BMP) -2 and -7 in the adjunct treatment of lower limb nonunions. Orthop Traumatol Surg Res 2018;104:1241-8. doi: 10.1016/j.otsr.2018.08.008.
12. Deng J, Wu J, Zhu Y. Inhibition of microRNA-9 improves fracture healing by modulating the bone morphogenetic protein-7 pathway. Pharmacology 2019;104:352-8. doi: 10.1159/000502402.
13. Ali AA, Mukhtar MM, Shaheen S, Mohamed AO. Assessment of plasma BMP-2, BMP-7, BMP-10, vitamin D, and TGF β1 in simple fractures among Sudanese patients. PLoS One 2021;16:e0247472. doi: 10.1371/journal.pone.0247472.
14. Lucotti S, Cerutti C, Soyer M, Gil-Bernabé AM, Gomes AL, Allen PD, et al. Aspirin blocks formation of metastatic intravascular niches by inhibiting platelet-derived COX-1/thromboxane A2. J Clin Invest 2019;129:1845-62. doi: 10.1172/JCI121985.
15. Chueh TH, Cheng YH, Chen KH, Chien CT. Thromboxane A2 synthase and thromboxane receptor deletion reduces ischaemia/reperfusion-evoked inflammation, apoptosis, autophagy and pyroptosis. Thromb Haemost 2020;120:329-43. doi: 10.1055/s-0039-3400304.
16. Courtois A, Makrygiannis G, Cheramy-Bien JP, Purnelle A, Pirotte B, Dogne JM, et al. Therapeutic applications of prostaglandins and thromboxane A2 inhibitors in abdominal aortic aneurysms. Curr Drug Targets 2018;19:1247-55. doi: 10.2174/1389450119666171227224314.
17. Udagawa N, Koide M, Nakamura M, Nakamichi Y, Yamashita T, Uehara S, et al. Osteoclast differentiation by RANKL and OPG signaling pathways. J Bone Miner Metab 2021;39:19-26. doi: 10.1007/s00774-020-01162-6.
18. Infante M, Fabi A, Cognetti F, Gorini S, Caprio M, Fabbri A. RANKL/RANK/OPG system beyond bone remodeling: Involvement in breast cancer and clinical perspectives. J Exp Clin Cancer Res 2019;38:12. doi: 10.1186/s13046-018-1001-2.
19. Dutka M, Bobiński R, Wojakowski W, Francuz T, Pająk C, Zimmer K. Osteoprotegerin and RANKL-RANK-OPG-TRAIL signalling axis in heart failure and other cardiovascular diseases. Heart Fail Rev 2022;27:1395-411. doi: 10.1007/s10741-021-10153-2.
20. Carrillo-López N, Martínez-Arias L, Fernández-Villabrille S, Ruiz-Torres MP, Dusso A, Cannata-Andía JB, et al. Role of the RANK/RANKL/OPG and Wnt/β-catenin systems in CKD bone and cardiovascular disorders. Calcif Tissue Int 2021;108:439-51. doi: 10.1007/s00223-020-00803-2.
21. Forde H, Davenport C, Harper E, Cummins P, Smith D. The role of OPG/RANKL in the pathogenesis of diabetic cardiovascular disease. Cardiovasc Endocrinol Metab 2018;7:28-33. doi: 10.1097/XCE.0000000000000144.
22. Amin N, Boccardi V, Taghizadeh M, Jafarnejad S. Probiotics and bone disorders: The role of RANKL/RANK/OPG pathway. Aging Clin Exp Res 2020;32:363-71. doi: 10.1007/s40520-019-01223-5.