Increasing serum miR-409-3p predicts the major adverse cardiac adverse events in elderly patients after hip fracture surgery

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Abstract

Background Major adverse cardiovascular events (MACE) are critical complications responsible for the morbidity and mortality of elderly hip fracture patients. There was an urgent need to explore an effect biomarker for predicting MACE in elderly patients receiving hip fracture surgery.

Objective This study focused on an age-related miRNA, miR-409-3p, and assessed its significance in elderly hip fracture patients.

Methods A total of 267 hip fracture patients were enrolled in this study including 104 elderly patients (age ≥ 60 years). All patients were followed up for 1 year to monitor the occurrence of MACE. The risk factors for the occurrence of MACE were evaluated by the logistic regression analysis.

Results Elderly age and reduced cardiac and renal function were identified as risk factors for MACE in hip fracture patients. Elderly patients also showed a high incidence of MACE. In elderly hip fracture patients, significant upregulation of miR-409-3p was observed, which was associated with patients' elderly age, higher level of revised cardiac risk index (RCRI), lower left ventricular ejection fraction (LVEF), and higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), creatine kinase-MB (CK-MB), and high sensitivity troponin I (hsTnI). Additionally, miR-409-3p was identified as an independent factor for the MACE in elderly patients received hip fracture surgery.

Conclusion Upregulated miR-409-3p was an age-related miRNA and could predict the occurrence of MACE in elderly hip fracture patients.

Keywords Hip fracture repair surgery, Postoperative complication, Cardiac and renal function, Major adverse cardiovascular disease

Introduction

The number of elderly people with hip fractures is gradually increasing year by year due to the accelerating aging of the population [1]. Surgical therapy could effectively alleviate pain and reduce the occurrence of complications and shorten the time in bed after the surgery [2]. Due to the complicated basic diseases, the prognosis of elderly patients who received hip fracture surgery is poor [3]. It was reported that the postoperative mortality rate of elderly patients receiving hip surgery was as high as 20-40%, where less than half of the survival patients could return to their pre-injury status [4]. The mortality is high within 1 year after surgery, and then the risk gradually decreases [5]. Previous studies have analyzed the independent factors for the postoperative mortality of hip fracture surgery, and aging, complications, and

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deferred operation were identified [6–8]. Major adverse cardiovascular events (MACE) are one of the most common complications and are important adverse prognostic factors for hip fracture surgery, which dramatically affects the postoperative life of elderly patients. Elderly patients are prone to MACE due to pathophysiological changes, such as reduced cardiac reserve capacity and degenerative changes in heart structure [9]. Hip fracture induced traumatic stress, pain, and other stimulations, which increase the risk of MACE, especially in the perioperative period [10]. The risk factors for MACE might be different from various research conditions and study subjects, and it is necessary to explore effect biomarkers that could predict MACE in elderly patients who received hip fracture surgery.

Thanks to the great progression made in molecular biology in the past decades, the significance of noncoding RNAs (ncRNAs) in human disease development has attracted huge attention [11]. Some studies identified aging-related ncRNAs that regulate cardiac diseases. For example, miR-217 was identified as an aging-related miRNA and has been demonstrated to promote atherosclerosis and cardiovascular dysfunction [12]. A previous study identified microRNA-409-3p (miR-409-3p) as an aging-related ncRNA that regulated the senescence of endothelial progenitor [13]. miR-409-3p was also suggested to regulate human cancer progression, such as breast cancer, cervical cancer, and osteosarcoma, and mediate chemotherapy and radiotherapy resistance [14, 15]. Additionally, miR-409-3p was also reported to regulate cardiac fibrosis and angiogenesis, and predict the development of heart failure [16–18]. Therefore, miR-409-3p was speculated to predict postoperative MACE in elderly patients with hip fracture, which was confirmed in the present study.

This study focused on the expression of miR-409-3p in elderly patients received hip fracture surgery. Based on the occurrence of postoperative MACE, the significance of miR-409-3p in predicting patients' disease development and MACE was evaluated, aiming to provide a potential biomarker for the outcomes of elderly patients with hip fracture.

Materials and methods
Study subjects
This is a retrospective study approved by the Ethics Committee of Linfen People's Hospital. A total of 267 hip fracture patients caused by low-energy trauma and receiving total hip replacement surgery were included, among which there were 104 elderly patients (age ≥ 60 years). The baseline information of study subjects has been summarized in Table S1. All patients have known about the study design and signed informed consent. The inclusion criteria were: 1) patients with neck of femur fracture, femoral intertrochanteric fracture, or subtrochanteric fracture of femur; 2) patients could walk independently or with the aids of tools before fracture; 3) patients received total hip replacement surgery; 4) patients with unilateral closed hip fracture induced by external force. Patients with one of the following items were excluded: 1) patients with a history of acute coronary syndrome, heart failure, or other cardiovascular diseases; 2) patients with pathological fractures; 3) patients with uncompleted clinical records; 4) patients who refuse follow-up surveys or close follow-up. The baseline information was collected from their clinical records.

Sample collection
Five milliliter fasting venous blood samples were collected from each participant before surgery and centrifugated at 3500 rpm for 10 min to isolate serum. Serum samples were stored at -80℃. The following analysis should be conducted within 48 h of sample collection.

Real-time quantitative PCR
Total RNA was extracted from serum samples using Trizol reagent (Invitrogen, USA) and evaluated by the ratio of OD260/280 (1.8-2.0). Reversed transcription was performed to generate cDNA with the TaqMan miRNA reverse transcription kit (Thermofisher Scientific, USA). PCR amplification was performed on the LightCycler 480 real-time PCR system (Applied Biosystem, USA) with the help of the SYBR Green kit, according to the manufacturer's protocol. The relative expression of miR-409-3p was calculated with the $2^{-\Delta\Delta CT}$ method with U6 as an internal reference.

Follow-up survey
A 1-year follow-up survey was conducted to summarize the occurrence of MACE in enrolled patients. The occurrence of one of the following events was defined as MACE: all-cause death, postoperative heart failure, postoperative atrial fibrillation, postoperative myocardial infarction, and cardiovascular re-hospitalization. The follow-up data were analyzed by Kaplan-Meier analysis and Cox regression analysis to identify risk factors for the occurrence of MACE in hip fracture patients, especially in elderly patients. There were no missing patients during the follow-up in this study.

Statistical analyses
A difference comparison between the two groups was performed with a student's t-test using SPSS 26.0 software. The occurrence of MACE was summarized by the Kaplan-Meier curve. The risk factors for MACE were evaluated by logistic regression analysis and Cox

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regression analysis. The association of miR-409-3p with patients' clinicopathological features was estimated by the Chi-square test. *P* < 0.05 indicates statistical significance.

Results

Aging is the risk factor for MACE in patients receiving hip fracture surgery

The enrolled patients were aged from 30 to 80 years with an average age of 55.69 ± 14.47 years. There were 104 elderly patients (age ≥ 60 years) included accounting for 38.95% of the study subjects. According to the 1-year follow-up survey, there were 91 occurred MACE after hip fracture surgery in the enrolled patients, including 13 dead cases (14.29%), 17 postoperative heart failure cases (18.68%), 14 postoperative atrial fibrillation cases (15.38%), 22 postoperative myocardial infarction cases (24.18%), and 25 cardiovascular re-hospitalization cases (27.47%). The incidence of MACE between different hip fracture types was not significantly different (data not shown). The results of logistic regression analysis showed that age was a risk factor for the occurrence of MACE (OR = 2.573, 95% CI = 1.277-5.182) together with other renal and cardiac function indexes, RCRI, LVEF, NT-proBNP, CK-MB, and hsTnI (Table 1). Consistently, the elderly patients showed a higher occurrence of MACE than that of patients aged < 60 (Fig. 1, Log-rank *P* = 0.0046).

Upregulated miR-409-3p in elderly patients was associated with the cardiac and renal function of elderly patients

In elderly patients, the serum miR-409-3p was significantly higher in patients occurring MACE than in patients without MACE (Fig 2a, *P* < 0.0001). Based on the mean value of serum miR-409-3p (1.40), patients were
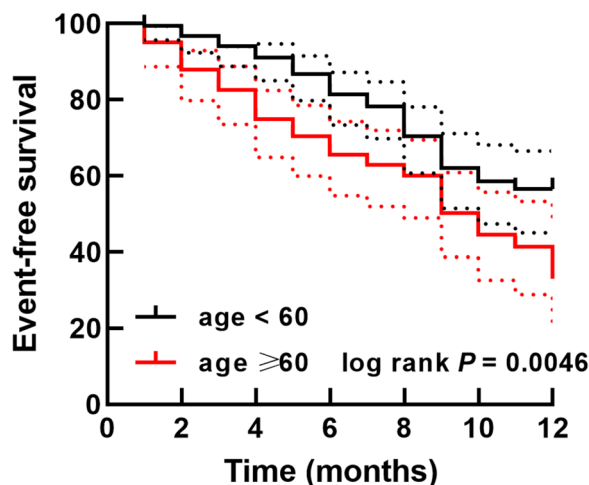

Fig. 1 Kaplan-Meier curve of the event-free survival of hip fracture patients based on age. The endpoints were defined as the occurrence of MACE, including all-cause death, postoperative heart failure, postoperative atrial fibrillation, postoperative myocardial infarction, and cardiovascular re-hospitalization with 90 d after surgery

grouped into the low-miR-409-3p and the high-miR-409-3p group. The higher serum miR-409-3p was associated with the elderly age (*P* = 0.019), the higher level of RCRI (*P* < 0.001), lower LVEF (*P* = 0.008), and the higher levels of cardiac and renal function indexes, NT-proBNP (*P* = 0.011), CK-MB (*P* < 0.001), and hsTnI (*P* < 0.001, Table 2).

Upregulated miR-409-3p predicted the occurrence of MACE in elderly patients

Patients in the high-miR-409-3p group were more likely to occur MACE than the patients in the low-miR-409-3p group (log-rank *P* = 0.026, Fig. 2b). Moreover, miR-409-3p was also identified as a predictor for MACE in elderly patients who received hip fracture surgery (HR = 2.454, *P* = 0.008) as well as RCRI (*P* = 0.044), LVEF (*P* = 0.045), NT-proBNP (*P* = 0.031), and CK-MB (*P* = 0.042, Table 3).

Discussion

MACE is one of the most common postoperative complications of hip fracture repair surgery, which significantly affects the recovery of patients [10, 19]. A previous study reported that the occurrence of heart failure in elderly patients who received hip fracture repair surgery reached up to 16% [20, 21]. However, another study found that the occurrence of MACE was 12% in elderly hip fracture patients [21, 22]. Therefore, the occurrence of MACE might be influenced by research location, time, and other factors. In this study, the occurrence and risk factors of MACE in patients receiving hip fracture repair

Table 1 Logistic regression analysis evaluating the risk factors for MACE in patients receiving hip fracture surgery

Features	95% confidence index	Odd ratios	*P*-value
Age	1.277–5.182	2.573	0.008
Sex	0.888–3.587	1.785	0.104
Smoking	0.801–3.625	1.704	0.166
Drinking	0.583–2.564	1.222	0.595
RCRI	1.495–6.378	3.088	0.002
LVEF	2.258–13.116	5.442	< 0.001
NT-proBNP	1.732–7.171	3.524	0.001
CK-MB	2.259–9.688	4.678	< 0.001
hsTnI	3.601–15.271	7.415	< 0.001

RCRI Revised cardiac risk index, *LVEF* Left ventricular ejection fraction, %, *NT-proBNP* N-terminal pro-Brainin natriuretic peptide, pg/mL, *CK-MB* Creatine kinase-MB, ng/mL; *hsTnI* High sensitivity troponin I, pg/mL

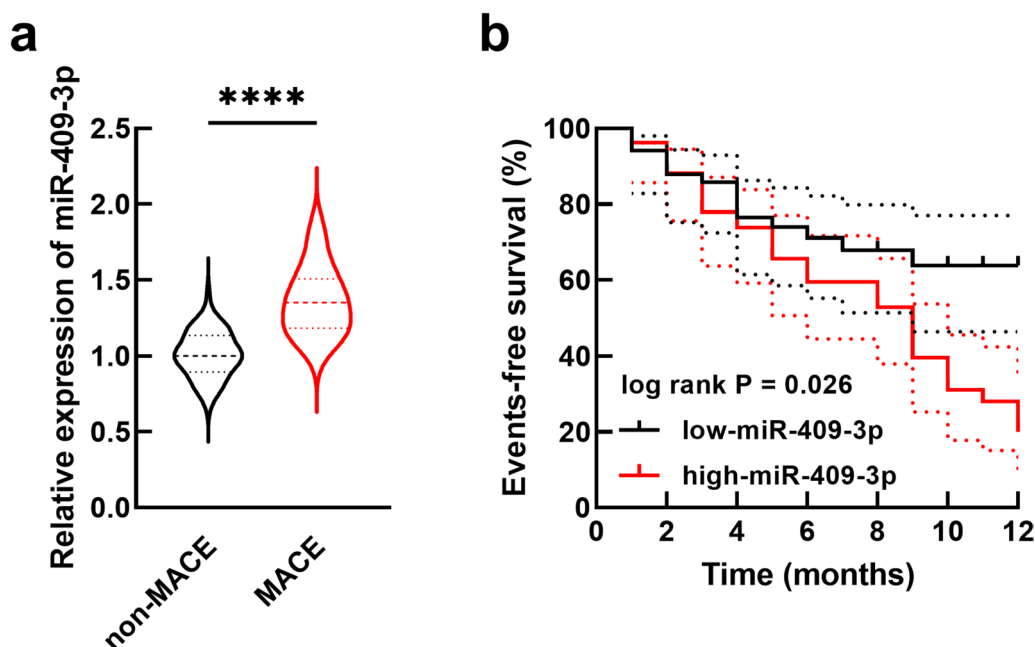Sun *et al. BMC Musculoskeletal Disorders*   (2023) 24:920

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Fig. 2 Expression of miR-409-3p in elderly hip fracture patients occurred MACE or not (a) and its correlation with the occurrence of MACE (event-free survival). ****$P < 0.0001$

surgery were investigated, where age was identified as a critical risk factor. The close association between age and MACE has been widely confirmed in previous studies. For example, a recent China research demonstrated that elderly ST-elevation myocardial infarction patients showed a 3.3-time increasing incidence of MACE than younger patients [23]. However, several studies found that the postoperative complications of hip replacement were not related to age, excluding MACE [24]. Additionally, except for age, the cardiac and renal function indexes were also identified as risk factors for MACE. Cardiac insufficiency is the main cause of MACE. On the one hand, perioperative pain, blood loss, and massive fluid rehydration enhance cardiac load and increase cardiac susceptibility. On the other hand, based on the original cardiac dysfunction of elderly patients, cardiac decompensation is more likely to occur [25, 26]. In addition, kidney dysfunction also increases cardiac load resulting in changes in the left atrium and ventricles and therefore induces the cardiac system [27, 28]. Therefore, the prediction of MACE should consider more basic conditions of patients, such as cardiac and renal function, and the significance of age should not be overestimated. It is also necessary to find a biomarker to provide a more accurate prediction of MACE.

Previously, the significance of miRNAs in predicting MACE in various patients has been widely reported. For instance, miR-126 was identified as a marker for indicating the occurrence of MACE in patients receiving percutaneous coronary intervention [29]. miR-146a-5p, miR-223-3p, and miR-142-3p were demonstrated to predict MACE in young patients with acute ST-elevation myocardial infarction [30]. These studies focused on the occurrence of MACE in cardiovascular diseases, there was a lack of biomarkers for predicting postoperative MACE in elderly patients receiving orthopedic surgery [19]. Herein, the significant upregulation of miR-409-3p was observed in elderly patients who received hip fracture repair surgery and occurred MACE. Upregulated miR-409-3p was associated with the elderly age and decreasing cardiac and renal function of patients. Patients with higher serum miR-409-3p levels were susceptible to MACE. miR-409-3p was identified to serve as an age-related miRNA, which is consistent with the results of this study [13]. Additionally, miR-409-3p was revealed to regulate cell progression and mediate cardiovascular and cerebrovascular diseases. The clinical significance of miR-409-3p in screening and monitoring disease development has also been widely noticed. For example, in atrial fibrillation patients, miR-409-3p showed a significant downregulation and was independently associated with disease onset and prognosis [31]. Reduced miR-409-3p was also identified as an indicator of the adverse outcomes of breast cancer patients [32]. The predictive value of miR-409-3p in elderly patients receiving hip fracture repair surgery suggested its potential to serve as a biomarker for MACE.

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Table 2 Correlation of miR-409-3p with elderly patients' clinicopathological features

	Total (*n* = 104)	Low-miR-409-3p	High-miR-409-3p	*P*-value
Age				0.019
<70	51	31	20	
≥70	53	20	33	
Sex				0.198
Male	67	36	31	
Female	37	15	22	
Smoking				0.531
Yes	44	20	24	
No	60	31	29	
Drinking				0.649
Yes	39	18	21	
No	65	33	32	
RCRI				<0.001
<3	49	33	16	
≥3	55	18	37	
LVEF				0.008
<50%	31	9	22	
≥50%	73	42	31	
NT-proBNP				0.011
<900	50	31	19	
≥900	54	20	34	
CK-MB				<0.001
<2.0	48	35	13	
≥2.0	56	16	40	
hsTnI				<0.001
<7.6	47	34	13	
≥7.6	57	17	40	

RCRI Revised cardiac risk index, *LVEF* Left ventricular ejection fraction, %, *NT-proBNP* N-terminal pro-Brainin natriuretic peptide, pg/mL, *CK-MB* Creatine kinase-MB, ng/mL, *hsTnI* High sensitivity troponin I, pg/mL

Table 3 Cox regression analysis evaluating the risk factors for MACE in elderly patients receiving hip fracture surgery

	95% CI	HR	*P*-value
miR-409-3p	1.269–4.744	2.454	0.008
Age	0.714–3.516	1.584	0.258
Sex	0.729–2.679	1.397	0.314
Smoking	0.822–2.902	1.544	0.177
Drinking	0.564–2.055	1.077	0.822
RCRI	1.021–5.054	2.271	0.044
LVEF	1.014–3.897	1.988	0.045
NT-proBNP	1.084–5.293	2.395	0.031
CK-MB	1.030–5.003	2.270	0.042
hsTnI	0.738–4.143	1.748	0.205

RCRI Revised cardiac risk index, *LVEF* Left ventricular ejection fraction, *NT-proBNP* N-terminal pro-Brainin natriuretic peptide, *CK-MB* Creatine kinase-MB, *hsTnI* High sensitivity troponin I

However, there are still many works need to be done in the future research. Previous extensive studies have demonstrated that early surgery could effectively reduce the occurrence of postoperative complications in patients with hip fracture, and most cases have also been considered emergency surgery [33]. All patients in the present study underwent surgery within 48 h of admission, and the significance of operation timing in predicting MACE was not evaluated. Future studies should include more patients with different surgery timing to clarify its importance in decreasing postoperative complications, especially reducing MACE.

In conclusion, age is a risk factor for the occurrence of MACE in patients with hip fracture. In elderly patients, upregulated miR-409-3p could predict the occurrence of MACE and was associated with patients' insufficient cardiac and renal function.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-023-07049-7.

Additional file 1: Table S1. Baseline information of study subjects.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All patients and their families were aware of this study and signed informed consent. This study was approved by the Ethics Committee of Linfen People's Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Xia J, Li Z, Zhao D, Hu Y, Lu X. Prevalence of frailty among elderly patients with hip fracture in China: protocol for a systematic review and meta-analysis. BMJ Open. 2023;13(10):e072623.
2. Li X, Gong X, He L, Wu X. Current surgical status of hip fracture among elderly in China. Injury. 2023:111083.
3. de Miguel Artal M, Roca Chacon O, Martinez-Alonso M, Serrano Godoy M, Mas Atance J, Garcia Gutierrez R. Hip fracture in the elderly patient: prognostic factors for mortality and functional recovery at one year. Rev Esp Geriatr Gerontol. 2018;53(5):247–54.
4. Bokshan SL, Marcaccio SE, Blood TD, Hayda RA. Factors influencing survival following hip fracture among octogenarians and nonagenarians in the United States. Injury. 2018;49(3):685–90.
5. Ekeloef S, Koyuncu S, Holst-Knudsen J, Gundel O, Meyhoff CS, Homilius M, et al. Cardiovascular events in patients undergoing hip fracture surgery treated with remote ischaemic preconditioning: 1-year follow-up of a randomised clinical trial. Anaesthesia. 2021;76(8):1042–50.
6. Barceló M, Torres OH, Mascaró J, Casademont J. Hip fracture and mortality: study of specific causes of death and risk factors. Arch Osteoporos. 2021;16(1):15.
7. Blanco JF, da Casa C, Pablos-Hernández C, González-Ramírez A, Julián-Enríquez JM, Díaz-Álvarez A. 30-day mortality after hip fracture surgery: Influence of postoperative factors. PLoS One. 2021;16(2):e0246963.
8. Sheehan KJ, Williamson L, Alexander J, Filliter C, Sobolev B, Guy P, et al. Prognostic factors of functional outcome after hip fracture surgery: a systematic review. Age Ageing. 2018;47(5):661–70.
9. Kim BS, Kim TH, Oh JH, Kwon CH, Kim SH, Kim HJ, et al. Association between preoperative high sensitive troponin I levels and cardiovascular events after hip fracture surgery in the elderly. J Geriatr Cardiol. 2018;15(3):215–21.
10. Hsu WWQ, Sing CW, Li GHY, Tan KCB, Cheung BMY, Wong JSH, et al. Immediate risk for cardiovascular events in hip fracture patients: a population-based cohort study. J Gerontol A Biol Sci Med Sci. 2022;77(9):1923–9.
11. Esteller M. Non-coding RNAs in human disease. Nat Rev Genet. 2011;12(12):861–74.
12. de Yebenes VG, Briones AM, Martos-Folgado I, Mur SM, Oller J, Bilal F, et al. Aging-Associated miR-217 Aggravates atherosclerosis and promotes cardiovascular dysfunction. Arterioscler Thromb Vasc Biol. 2020;40(10):2408–24.
13. Lee YN, Wu YJ, Lee HI, Wang HH, Hung CL, Chang CY, et al. Hsa-miR-409-3p regulates endothelial progenitor senescence via PP2A-P38 and is a potential ageing marker in humans. J Cell Mol Med. 2023;27(5):687–700.
14. Yu X, Fu X, Zhang X, Bai C, Wang Y. Circ_0001658 regulates gefitinib resistance of non-small cell lung cancer through miR-409-3p/TWIST1 axis. Anticancer Drugs. 2022;33(2):158–66.
15. Becker-Greene D, Li H, Perez-Cremades D, Wu W, Bestepe F, Ozdemir D, et al. MiR-409-3p targets a MAP4K3-ZEB1-PLGF signaling axis and controls brown adipose tissue angiogenesis and insulin resistance. Cell Mol Life Sci. 2021;78(23):7663–79.
16. Wang C, Yin S, Wang Q, Jiang M, Li S, Zhen W, et al. miR-409-3p regulated by GATA2 promotes cardiac fibrosis through targeting Gpd1. Oxid Med Cell Longev. 2022;2022:8922246.
17. Bestepe F, Fritsche C, Lakhotiya K, Niosi CE, Ghanem GF, Martin GL, et al. Deficiency of miR-409-3p improves myocardial neovascularization and function through modulation of DNAJB9/p38 MAPK signaling. Mol Ther Nucleic Acids. 2023;32:995–1009.
18. Chen MC, Chang TH, Chang JP, Huang HD, Ho WC, Lin YS, et al. Circulating miR-148b-3p and miR-409-3p as biomarkers for heart failure in patients with mitral regurgitation. Int J Cardiol. 2016;222:148–54.
19. Araguas MA, Herrera A, Garrido I, Mateo J, Mayoral AP, Munoz M. Risk factors for major adverse cardiovascular events after osteoporotic hip fracture repair surgery. Injury. 2020;51(Suppl 1):S30–6.
20. Wei S, Pan W, Lee C, Tsumura H, Xue TM, McConnell ES. Heart failure and hospital utilization trajectories before and after hip fracture surgery. J Am Med Dir Assoc. 2022;23(11):1884-5.e1.
21. You F, Ma C, Sun F, Liu L, Zhong X. The risk factors of heart failure in elderly patients with hip fracture: what should we care. BMC Musculoskelet Disord. 2021;22(1):832.
22. Lee R, Lee D, Gowda NB, Probasco WV, Ibrahim G, Falk DP, et al. Surgical complications associated with congestive heart failure in elderly patients following primary hip hemiarthroplasty for femoral neck fractures. Eur J Orthop Surg Traumatol. 2019;29(6):1253–61.
23. Wang C, Zhou L, Liang Y, Liu P, Yuan W. Interactions of ST-elevation myocardial infarction, age, and sex and the risk of major adverse cardiovascular events among Chinese adults: a secondary analysis of a single-centre prospective cohort. BMJ Open. 2022;12(7):e058494.
24. Toro G, Bothorel H, Saffarini M, Jacquot L, Chouteau J, Rollier JC. Uncemented total hip arthroplasty in octogenarian and nonagenarian patients. Eur J Orthop Surg Traumatol. 2019;29(1):103–10.
25. Chen X, Ma Y, Deng Z, Li Q, Liao J, Zheng Q. Prediction of early postoperative major cardiac events and in-hospital mortality in elderly hip fracture patients: the role of different types of preoperative cardiac abnormalities on echocardiography report. Clin Interv Aging. 2020;15:755–62.
26. Li M, Chen C, Shen J, Yang L. Preoperative hemoglobin <10 g/DL predicts an increase in major adverse cardiac events in patients with hip fracture over 80 years: a retrospective cohort study. Geriatr Orthop Surg Rehabil. 2023;14:21514593231183612.
27. Fu EL, Evans M, Carrero JJ, Putter H, Clase CM, Caskey FJ, et al. Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. BMJ. 2021;375:e066306.
28. Giugliano D, De Nicola L, Maiorino MI, Bellastella G, Garofalo C, Chiodini P, et al. Preventing major adverse cardiovascular events by SGLT-2 inhibition in patients with type 2 diabetes: the role of kidney. Cardiovasc Diabetol. 2020;19(1):35.
29. Poivret D, Goetz C, Zevering Y, Wilcke C, Noirez V. Effect of patient-led cooperative follow-up by general practitioners and community pharmacists on osteoporosis treatment persistence. Int J Rheum Dis. 2021;24(7):912–21.
30. Scarlatescu AI, Barbalata T, Sima AV, Stancu C, Niculescu LS, Micheu MM. miR-146a-5p, miR-223-3p and miR-142-3p as Potential Predictors of Major Adverse Cardiac Events in Young Patients with Acute ST Elevation Myocardial Infarction-Added Value over Left Ventricular Myocardial Work Indices. Diagnostics (Basel). 2022;12(8):1946–63.
31. Liu T, Zhong S, Rao F, Xue Y, Qi Z, Wu S. Catheter ablation restores decreased plasma miR-409-3p and miR-432 in atrial fibrillation patients. Europace. 2016;18(1):92–9.
32. Cao GH, Sun XL, Wu F, Chen WF, Li JQ, Hu WC. Low expression of miR-409-3p is a prognostic marker for breast cancer. Eur Rev Med Pharmacol Sci. 2016;20(18):3825–9.
33. Bhatti UF, Shah AA, Williams AM, Biesterveld BE, Okafor C, Ilahi ON, et al. Delay in hip fracture repair in the elderly: a missed opportunity towards achieving better outcomes. J Surg Res. 2021;266:142–7.