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MINIREVIEWS

Quality of life and functional capacity in patients after cardiac surgery intensive care unit

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Abstract

Coronary heart disease and aortic stenosis are prevalent cardiovascular diseases worldwide, leading to morbidity and mortality. Coronary artery bypass grafting (CABG) and surgical aortic valve replacement (SAVR) have therapeutic benefits, including improved postoperative quality of life (QoL) and enhanced patient functional capacity which are key indicators of cardiac surgery outcome. In this article, we review the latest studies of QoL outcomes and functional capacity in patients who underwent cardiac surgery. Many standardized instruments are used to evaluate QoL and functional conditions. Preoperative health status, age, length of intensive care unit stay, operative risk, type of procedure, and other pre-, intra-, and postoperative factors affect postoperative QoL. Elderly patients experience impaired physical status soon after cardiac surgery, but it improves in the following period. CABG and SAVR are associated with increases of physical and mental health and functional capacity in the immediate postoperative and the long long-term. Cardiac rehabilitation improves patient functional capacity, QoL, and frailty following cardiac surgery.

Key Words: Quality of life; Health-related quality of life; Functional capacity; Cardiac rehabilitation; Cardiac surgery; Coronary artery bypass grafting; Heart valve surgery; Heart valve replacement

Core Tip: Health-related quality of life (QoL) and functional capacity are the main indicators of patient outcome after cardiac surgery. Preoperative health condition, age, length of intensive care unit (ICU) stay, operative risk, type of procedure, perioperative complications and comorbidities are the primary determinants of QoL after ICU discharge. Following heart surgery, the physical status of elderly patients is lower than that of younger patients but improves over time. The results of studies of patient health status and functional ability after cardiac surgery reveal significant short- and long-term improvement of QoL and functional capacity. Cardiac rehabilitation has a central role in the recovery of function.

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INTRODUCTION

Cardiovascular diseases are among the leading causes of morbidity and mortality worldwide[1,2]. They account for 17.9 million deaths annually[3], increase in occurrence with age, and coronary heart disease and aortic stenosis are among the most common[4-6]. However, effective prevention, treatment, and management decrease the incidence and the risk of sudden cardiac death[2]. Surgical intervention by coronary artery bypass grafting (CABG) and surgical aortic valve replacement (SAVR), which are primarily performed in elderly patients[7], increase survival, functional status, and quality of life (QoL)[3,8,9]. The current revision of the European Society of Cardiology/European Association for Cardio-thoracic Surgery (ESC/EACTS) recommendations on managing valvular heart disease include considering the patient's anticipated life expectancy and QoL when planning interventions in elderly patients[10].

Elderly patients undergoing cardiac surgery pose a significant challenge as they have a greater incidence of comorbidities and are at a high risk of readmission, mortality, and development of complications. Patients with cardiac procedures and an ICU stay of at least 5 days had a 1-year overall survival rate of 46.2%, and those who were discharged had a 1-year survival rate of 72.4%[11]. In another study[12], the overall survival rate was 67.8% 10 years after surgery. Patients over 75 years of age had lower survival rates than younger patients (44.6% *vs* 74.6%, $P < 0.001$).

QoL is a subjective perception of an individual's well-being, and is influenced by sociocultural factors. The ability to carry out daily activities, including of physical mobility, independence from others, sufficient energy for self-help, social contacts, emotional stability, absence of pain or other symptoms of discomfort, and adequate sleep and rest, are indicators of a high QoL[3,13]. QoL is an important outcome of cardiac surgery as it helps predict surgical success from the viewpoint of both patients and surgeons and it is affected by preoperative and postoperative factors[14]. Following cardiac surgery, patients frequently experience pain, discomfort, depressive symptoms, frailty, a loss of overall well-being, and an inability to return to their pre-procedure level of functioning. These symptoms may considerably reduce QoL.

Functional capacity is also affected postoperatively because respiratory abnormalities may decrease peripheral muscle strength and physical activity[14]. Patients experience decreased muscle strength and functional capacity[15] as well as pulmonary complications such as pneumonia, atelectasis, and pleural effusion after CABG[16]. Improving functional status is a key objective in addition to increasing survival. Early mobilization after cardiac surgery appears limited, with a significant trend to increase over ICU stay, and is related to decreased duration of mechanical ventilation and ICU length of stay[17]. Enrollment in cardiac rehabilitation (CR) programs improves functional capacity and decreases mortality, complications, length of postoperative stay, and readmission rate[18-21]. The benefits of alternative exercise modalities, such as neuromuscular electrical stimulation, are increased muscle strength and improved muscle function, but have no significant effect on functional capacity[22]. The aim of this review is to provide an overview of the most recent findings on QoL and functional capacity in patients after heart surgery.

ASSESSMENT TOOLS

QoL instruments

Health status instruments aim to provide a comprehensive assessment of health-related QoL (HRQoL) and can be used to compare various patient cohorts, conditions, and subsequent treatments (Figure 1). The 36-Item Short-Form Health Survey (SF-36) is a standardized tool for evaluating QoL[23], and offers valuable insights when used in patients undergoing cardiac surgery[4,8,12,24]. It consists of 36 multiple-choice questions measuring eight different health-related dimensions. The scores of each item in every dimension are recorded and transformed into a scale ranging from 0 (worst health status) to 100 (best health status), with increasing scores representing improved QoL outcomes[25]. The 12-Item Short Form Health Survey (SF-12) is another generic health status measure, two-component summary scales of mental

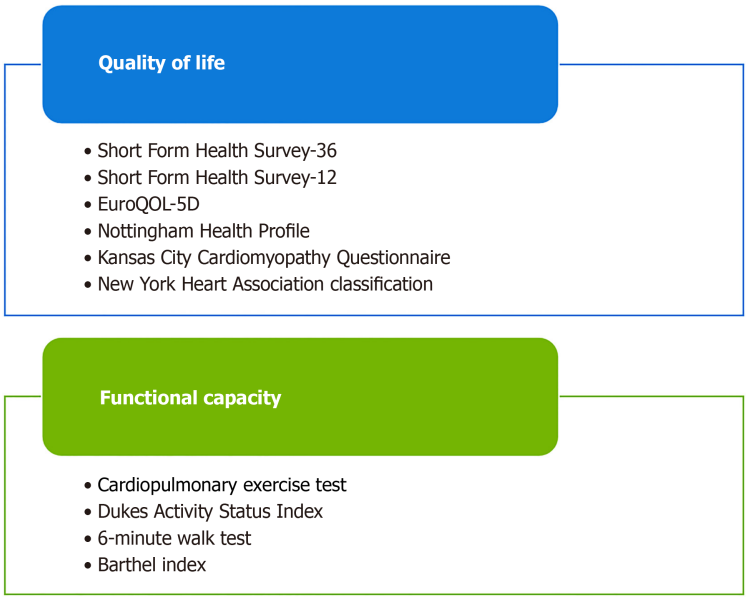

Figure 1 Assessment tools for the evaluation of quality of life and functional capacity.

and physical HRQoL are generated. It includes 12 questions from the original SF-36 health survey, and two-component summary scales of mental and physical HRQoL are generated by scoring, combining, and weighing the standardized responses[26].

The EuroQOL-5D scoring system assesses the cost-benefit or cost-effectiveness of a particular procedure or treatment [4]. It is a descriptive model that characterizes health in terms of five dimensions, namely mobility, self-care, daily activity, pain/discomfort, and anxiety/depression. Each dimension is scored as having no problems, some problems, or extreme problems. The instrument is a self-completed questionnaire that allows respondents to rate their general health on the day of the interview using a vertical visual analog scale with a hash mark system that ranges from 0 to 100, representing the worst and best possible states of health, respectively[27].

The Nottingham Health Profile questionnaire is a generic scale designed to identify indicators of health limitations rather than quantify disease severity. It contains 38 questions grouped into six domains[28]. The Kansas City Cardiomyopathy Questionnaire is a self-administered 23-item questionnaire designed to independently assess a patient's perception of their health status, including heart failure symptoms, impact on physical and social function, and how their heart failure affects their QoL[29].

Functional status assessment

Cardiopulmonary exercise testing (CPET) is considered the gold standard noninvasive assessment of cardiopulmonary disorders, especially heart failure. It evaluates the pulmonary, cardiovascular, muscular, and cellular oxidative responses to exercise. CPET determines maximum exercise capacity by measuring peak oxygen uptake, and has prognostic and diagnostic applicability for cardiorespiratory fitness[30]. It is also an effective means to evaluate the therapeutic benefit of cardiac surgery in patients after CABG[31] or enrollment in CR[21].

The Duke Activity Status Index (DASI) is a self-administered questionnaire used to measure functional capacity[32], and it has been validated in patients with cardiovascular disease[33,34]. A 12-item scale weighs the metabolic costs of daily activities such as personal care, ambulation, household tasks, sexual function, and recreation. The summation of positive responses yields a total score ranging from 0 to 58.2, with higher scores indicating greater functional capacity[32].

The 6-Minute Walk Test evaluates cardiopulmonary functional capacity and is used to determine the effects of therapeutic interventions and prognosis of patients undergoing heart surgery, including CABG and aortic or and mitral valve replacement[15,20,31,34-36]. The test consists of the distance walked as quickly as possible without running for 6 min in a 30-m hallway.

The Barthel mobility index is an ordinal scale that measures the ability to complete activities of daily living. Ten items are scored by summing the points awarded to each daily life skill, such as eating, transferring, grooming, toileting, bathing, dressing, walking, climbing stairs, and incontinence (bladder and bowel). The values range from 0 to 100, with increasing scores indicating improved independence in performing daily activities[11,37,38].

HRQoL

Predictors of QoL

Several studies have investigated the potential risk factors affecting QoL after cardiac surgery. The existing evidence identified 62 preoperative, 5 intra-operative, and 36 postoperative independent predictors of HRQoL shown in Figure 2

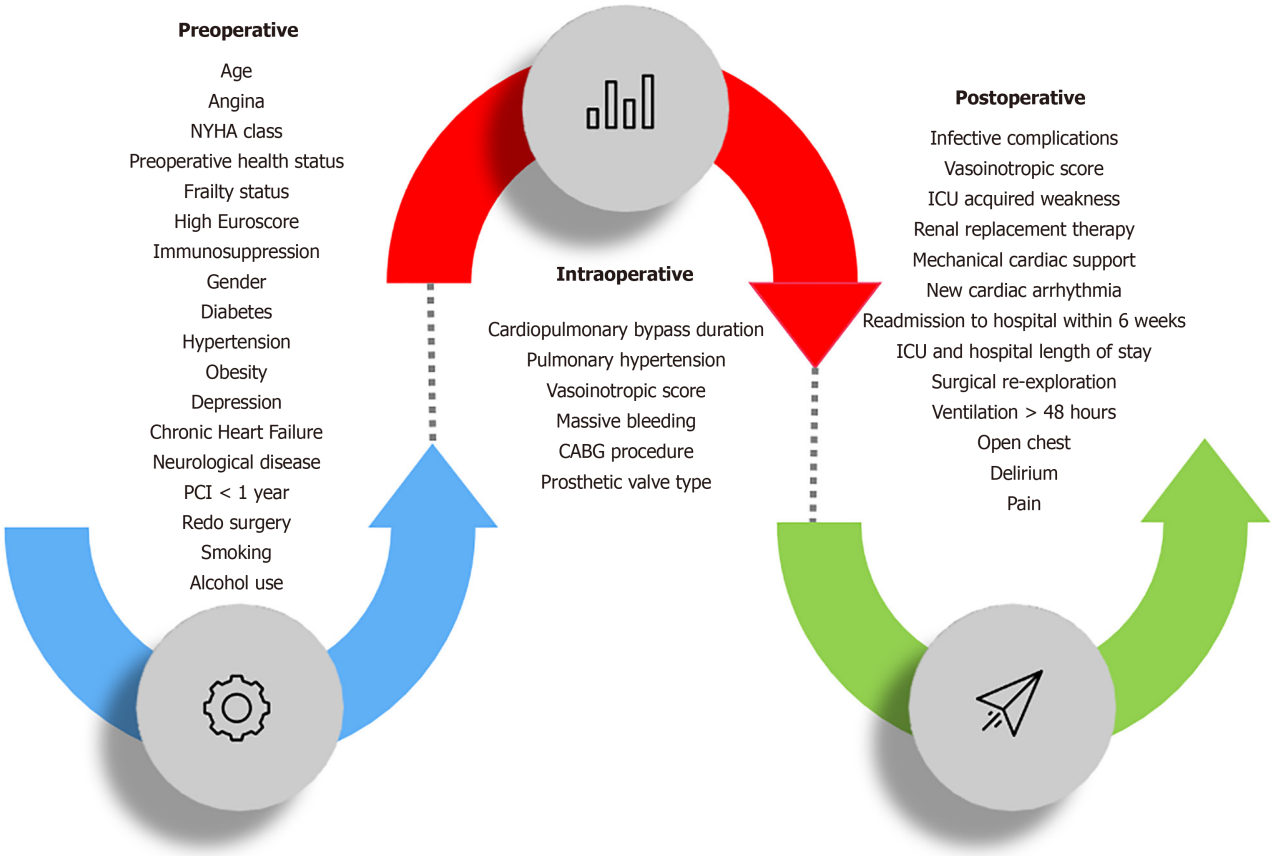

Figure 2 Pre-, intra- and postoperative predictors of health-related quality of life after cardiac surgery. CABG: Coronary artery bypass grafting; ICU: Intensive care unit; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention.

[14]. Alcohol use, body mass index, body weight, depression, preoperative health status, and smoking are potential modifiable predictors of HRQoL outcomes after cardiac surgery[14]. Preoperative health status was identified as a predictor of worsening postoperative HRQoL 1 year after surgery[39]. Low preoperative HRQoL increased the odds of worse physical health after surgery, and improved mental health was associated with better preoperative physical health and worse preoperative mental health[40]. CABG was a predictor of deterioration of mental health, and previous neurological disease was found to be a negative predictor of physical health[39]. Noyez *et al*[41] reported the same correlations between pre- and postoperative QoL, with age and operative risk indicating deterioration of postoperative QoL. On-pump CABG had an effect on QoL similar to that of off-pump procedures 6 months and 18 months after surgery[42, 43] and to that of CR outcomes[44].

Perioperative management with administration of fluid, inotropes, mechanical ventilation strategies, and postoperative secondary preventive care significantly reduces morbidity, mortality, and duration of hospital stay and improves patient QoL[45,46]. In the postoperative period, pain, traumatic memories, and restlessness in the ICU are independent predictors of QoL. Muscle mass shows a trend of decrease in post-cardiac surgery patients and is associated with a prolonged duration of mechanical ventilation and length of ICU stay[47]. Predictors of HRQoL outcome are potentially modifiable[14]. Moreover, the incidence of postoperative delirium and infections is higher in octogenarians after SAVR than in patients younger than 80 years of age. However, there is no difference in operative mortality and long-term survival[7,24].

Recovery time after surgery is an independent predictor of an improvement in HRQoL. Except for the mitral valve, valve replacement predicts improvement of the subscales of physical function and general health. Furthermore, postoperative HRQoL deteriorates with increasing age[8]. The domains of role–physical, body pain, and vitality decrease by a one-third point with every 1 year increase in age. Sex was also a significant predictor, with an average of 13-point less improvement in the role-emotional domain in men than in women[48]. However, Pačarić *et al*[3] found that age, sex, lifestyle, and risk factors did not predict poor QoL in CABG patients after rehabilitation.

QoL and CABG

For elderly patients, functional independence and improved QoL after cardiac surgery may be more important than extending life expectancy. There seems to be a correlation between QoL and patients' age 6 months after CABG[49]. Patients who were 60-69 years of age had the most significant improvement of all QoL domains compared to those < 50, 50-59, and ≥ 70 years of age. Another study found that the trajectories of SF-36 scores revealed that HRQoL and function had improved in the 10 years after cardiac surgery; the improvements of physical and social functioning and role limitations caused by physical problems were smaller in patients older than 75 years of age[12] (Table 1).

Table 1 Characteristics of studies that evaluated patient outcomes after coronary artery bypass grafting and other cardiac surgery

Ref.	Study design	Purpose	Population (*n*)	Male/female; age in yr	Cardiopulmonary bypass time in min/X-clamp time in min	Intervention	Outcomes	Main results
Deschka *et al* [11], 2013	Observational study	To assess survival, functional capacity, and QoL 1 year after cardiac surgery	CABG, HVS, combined procedures, aortic surgery, miscellaneous, emergency procedures (119)	84/35; 72.2 ± 9.3	NA	Barthel mobility index, SF-12 questionnaire	Long-term ICU treatment after cardiac surgery is related to a high in-hospital and follow-up mortality	In-hospital: Mortality was 36.1%, 1-year overall survival was 46.2%, and 1-year survival of the discharged patients was 72.4%. Preoperative Barthel mobility index was 94.7% ± 13.9% *vs* 85.2% ± 23.0% postoperatively. QoL was comparable with the normative population
Peric *et al*[49], 2015	Observational study	To evaluate the changes in QoL 6 months after CABG surgery related to the patients' age	CABG (226)	181/45; 58.3 ± 8.3/61.6 ± 6.1	On pump procedure	NHP questionnaire part 1 before and 6 months after surgery	Improvement of QoL after 6 months in older patients. Age is not an independent predictor of QoL deterioration after CABG	Before CABG elderly patients had worse QoL in sections of PM (r = 0.22, P = 0.001), SI (r = 0.16, P = 0.009) and En (r = 0.23, P = 0.001). After 6 months, patients group < 50 years improved in sections of PM, En, pain, and sleep. Group 60-69 years improved in all sections. Group 50-59 years and ≥ 70 years also improved in all sections except SI and sleep respectively. There was a significant relationship between patient's age and improvement of QoL in sections of PM (r = 0.18, P = 0.008), SI (r = 0.17, P = 0.01) and En (r = 0.21, P = 0.002)
Westerdahl *et al* [51], 2016	Prospective study	To investigate pulmonary function and HRQoL 1 year after cardiac surgery	CABG, HVS, or combined surgery (150)	123/27; 66 ± 9	112 ± 53/84 ± 46	SF-36 questionnaire, pulmonary function measurements	HRQoL improved in comparison to preoperative values. Static and dynamic lung function measurements slightly decreased, levels of pain were low, and saturation of peripheral oxygen was same as preoperatively	HRQoL improved in all 8 aspects of SF-36 (P < 0.001). FVC decreased by 4%-5% compared to preoperative values (P < 0.05). Sternotomy-related pain at rest was 0 (0-7), at deep breath 0 (0-4) and at coughing 0 (0-8)
Gjeilo *et al*[12], 2018	Prospective, observational cohort study	To assess survival, functional status, and HRQoL 10 years after cardiac surgery	Isolated CABG, HVS, CABG with HVS, miscellaneous (274)	228/46; 64.1 ± 9.9	64.0 (range: 16.0-206)/40.0 (5.0-180.0)	SF-36 questionnaire NYHA classification	HRQoL and function improved from before to 10 years after cardiac surgery, also for older patients	Total survival at 10 years was 67.8%. HRQoL improved compared with baseline in 7 of 8 SF-36 subscales. Older patients improved less than younger patients (3 of 8 SF-36 subscales were worse). NYHA classification improved also among older patients (from 59% in NYHA class III/IV at baseline to 30.3% after 10 years, P < 0.013)
Joskowiak *et al* [39], 2022	Prospective cohort study	To assess HRQoL change within 12 months after cardiac surgery and to identify predictors of deterioration in physical and mental health	CABG, AVR, CABG and AVR, aortic surgery, other surgery, redo surgery (164)	123/41; 70 (range: 62-76)	122.9 ± 37.4/81.8 ± 27.6	SF-36 questionnaire upon admission and at 3 months and 12 months after surgery	Gradual improvement of physical and mental health status	PCS score increased from 40.1 (range: 31.9-49.9) before surgery to 46.3 (37.0-52.4) at 3 months and 52.4 (46.4-56.3) at 12 months after surgery. The MCS score increased from 48.8 (38.6-55.3) at baseline to 50.9 (38.9-57.2) at 3 months and 53.1 (42.0-57.8) at 12 months after surgery. Up to 7.9% and 21.2% of patients had poorer PCS and MCS scores respectively at 12 months. Predictors of deterioration in postoperative HRQoL

							are preoperative health status, age < 70 years, CABG and a previous neurological event
Muthukrishnan *et al*[50], 2023	Prospective cohort study	To determine the QoL 3 months after CABG surgery	CABG (200)	184/16; 55 (12.5)	SF-36 questionnaire and STAI scale 2 days before and 3 months after CABG surgery	Improvement in physical health. Preoperative anxiety was a significant predictor of physical health	PCS score was 34.57 ± 9.6 preoperative *vs* 43.53 ± 7 postoperative. MCS score respectively was 54.87 ± 1.19 *vs* 51.65 ± 9.67. Perception of low physical health QoL was due to preoperative anxiety (β = 0.535, t = 8.433, P < 0.001)

AVR: Aortic valve surgery; CABG: Coronary artery by-pass grafting; CAD: Coronary artery disease; En: Energy; FVC: Forced vital capacity; HRQoL: Health-related quality of life; HVS: Heart valve surgery; MCS: Mental component summary; NA: Not available; NYHA: New York Heart Association; PCS: Physical component summary; PM: Physical mobility; QoL: Quality of life; SI: Social isolation; STAI: State-trait anxiety inventory; SF-36: Short-Form Health Survey-36.

Studies of the QoL after CABG have yielded encouraging short-and long-term results. Although preoperative anxiety was a strong predictor of poor HRQoL, patients had greater increases of the level of physical health compared with mental health 3 months after CABG[50]. This is within the range of the findings of another study, where physical and mental component summary scores increased for the majority of patients at 12 months after surgery. However, one-third of patients at 3 months and one-fifth of patients at 1 year did not recover their mental health status[39].

Deschka *et al*[11] assessed survival, functional outcome, and QoL 1 year after discharge from the hospital in patients who had been treated for at least 5 days. The physical and mental health scores in the SF-12 health survey did not differ from a normative sample. HRQoL also significantly increased 1 year after surgery in all eight SF-36 trajectories in 150 patients undergoing CABG, valve surgery, or combined surgery[51]. Long-term positive health status results were also reported by Gjeilo *et al*[12], with improvement of seven of eight SF-36 subscales 10 years after obtaining the baseline values.

QoL and heart valve surgery

QoL after valve surgery has been the focus of interest in many studies. SAVR procedures in octogenarians have low postoperative mortality. However, QoL was found to decrease 30 days after surgery and then improve to or above normal at the 1-year follow-up (Table 2). Additionally, age did not seem to affect physical or mental health during the reported period[24]. Improvement in the QoL of frail patients after 3 months was reported by Kotajarvi *et al*[34], with increases of physical function and physical health of 50% in the DASI and 14% in the SF-12 scores. In the frail compared with non-frail patients, mental health (3.6 points *vs* < 1 point), well-being (21.6 points *vs* 7.1 points), and QoL (25.1 points *vs* 8.7 points) improved significantly in frail compared with non-frail patients.

HRQoL was increased at 6 months after the SAVR procedure except in the bodily pain dimension of SQ-36. The EQ-5D index increased from 0.73 to 0.90, as did the visual analog scale score[25]. At 12 months of follow-up after SAVR and CABG, the results converged, with improvements in QoL within each group[52]. Over 2 years of follow-up the health status of patients with severe aortic stenosis after SAVR also increased considerably[29].

In a study with a follow-up of 5.9 years, there was a noticeable increase across the subscales of the SF-36 except for mental health in patients after heart valve replacement. At 1 year, there was an improvement across all domains except for mental health. At 2 years, health status increased from the preoperative measurement, with mental health being significantly better. However, physical function, role-physical, and role-emotional domains were significantly reduced compared with the 1 year outcomes. After 2 years, all SF-36 trajectories other than mental health showed significant increases compared with the preoperative values[48]. In an observational study of 899 patients, mean physical health

Table 2 Characteristics of the studies reviewed for patients after heart valve surgery

Ref.	Study design	Purpose	Population (*n*)	Male/female (*n*); age in yr	X-clamp time in min	Intervention	Outcomes	Main results
Thomson Mangnall *et al*[48], 2014	Prospective study	To evaluate the HRQoL after heart valve replacement surgery	Rheumatic heart disease (128)	56/72; 26.7 (12.4)	NA	SF-36 questionnaire (preoperatively and 1, 2, and > 2 years postoperatively)	Significant improvement of HRQoL sustained over time	Preoperative HRQoL was impaired but at 1 year postoperative improved across all domains ($P < 0.05$) apart from mental health ($P = 0.081$). At 2 years it remained improved from preoperative measurement, with mental health now significantly better ($P = 0.028$). By > 2 years follow-up all HRQoL domains, except for mental health, were significantly better than preoperative ($P = 0.066$)
Jansen Klomp *et al* [24], 2016	Prospective, observational cohort study	To investigate the influence of age on postoperative outcomes and HRQoL 1 year after SAVR	AS age < 80 (597) and AS age ≥ 80 (163)	363/234 and 85/78; 71 (range: 66-75) and 82 (81-83)	91 (range: 75-111) and 82 (68-107)	SF-36 questionnaire (PCS and MCS score)	Mortality rates were low in group ≥ 80 years and QoL increased towards normal values	In octogenarians, postoperative delirium was 11.0% *vs* 6.2% in < 80 years; $P = 0.034$. Operative mortality was 1.9% *vs* 2.9%; $P = 0.59$. The QoL was impaired 30-days after surgery (PCS = 45.01, $P < 0.001$; MCS = 48.21, $P = 0.04$) but improved towards or above normal values at 1-year follow-up (PCS = 49.92, $P = 0.67$, MCS = 52.55, $P < 0.001$). Age was not associated with a lower PCS ($\beta = 0.08$ per year, $P = 0.34$) or MCS ($\beta = 0.08$ per year, $P = 0.32$) 1 year after surgery
Baron *et al* [29], 2017	Randomized clinical trial	To compare HRQoL among intermediate-risk patients with severe AS treated with either TAVR or SAVR	TAVR (950) and SAVR (883)	1006/827; 81.4 (6.8)	NA	KCCQ, SF-36 questionnaire and EuroQOL-5D at baseline, 1 month, 1 year, and 2 years	Improvement of health status with both TAVR and SAVR at 2 years of follow up	After 2 years of follow up, both TAVR and SAVR showed significant improvements in both disease-specific (16-22 points on the KCCQ-OS scale) and generic health status (3.9-5.1 points on the SF-36 physical summary scale)
Kotajarvi *et al*[34], 2017	Prospective study	To investigate QoL in patients undergoing TAVR or SAVR, and examine the extent to which patient-centered outcomes compare between frail and non-frail patients	AS (103)	61/42; 80.6 ± 7.4	NA	DASI, SF-12 questionnaire and LASA administered before and 3 months after surgery	Frail patients exhibit greater improvement in patients' self-reported outcomes than non-frail patients	Frail patients improved in DASI and SF-12 PCS scores by 50% and 14%, respectively. SF-12 MCS scores improved in frail compared to non-frail participants (3.6 points *vs* < 1 point). Physical well-being and QoL measures also increased in frail compared to non-frail participants (21.6 points *vs* 7.1 points) and (25.1 points *vs* 8.7 points) respectively
Olsson *et al* [25], 2017	Single-center study	To describe patients' self-reported outcomes in terms of physical function, symptoms, dependence, HRQoL, and cognitive function after TAVI and SAVR	TAVI (24) and SAVR (24)	15/9 and 12/12; 81 (range: 60-90) and 80 (61-88)	NA	Katz index of independence in ADL, SF-36 questionnaire, EuroQOL-5D and Mini Mental State Examination on the day before and at 6 months after surgery	No change in cognitive function or dependence and no difference in the size of improvement between groups at 6 months' follow-up	Symptoms reduced, but breathlessness and fatigue remained, especially in the TAVI group. HRQoL was very low in the TAVI group at baseline but increased in all dimensions except social function
Blokzijl *et al* [8], 2021	Observational, multicenter, cohort study	To explore the effect of SAVR on QoL and the variance with age	SAVR (899)	583/316; NA	NA	SF-12 or SF-36 questionnaire at baseline and at 1-year follow-up	Patients after SAVR on average improve in physical and mental QoL	Physical health increased from 55 to 66 and mental health from 60 to 66
Surman *et al*[52], 2022	Prospective study	To report on the prospective outcomes in the areas of depression, QoL, angina, and frailty in SAVR and TAVR patients with AS	TAVR (100), SAVR (100), and CABG (100)	79/21, 80/20, 79/21; 65.94 (11.6), 82.87 (6.9), 65.90 (10.0)	NA		Improvement in PROMs and frailty in all groups by 3 months postoperative regardless of type of surgery	QoL improved within each group over 12 months (P value = 0.0001). Depression between groups (P value = 0.0395) and within each group was significant (P value = 0.0073 for SAVR and 0.0001 for TAVR). Angina was most frequent in TAVR in the QL ($P = 0.0001$) and PL ($P = 0.0007$) domains, and

	improvement was significant in the QL (SAVR P = 0.0010, TAVR P = 0.0001) and PL (SAVR P = 0.0002, TAVR P = 0.0007) domains in both groups. Frailty improved in both groups but was greatest in TAVR (P = 0.00126)

ADL: Activities of daily life; AS: Aortic stenosis; CABG: Coronary artery bypass grafting; DASI: Duke Activity Status Index; HRQoL: Health-related quality of life; KCCQ: Kansas City Cardiomyopathy Questionnaire; LASA: Linear analogue self-assessment; MCS: Mental component score; NA: Not available; PCS: Physical component score; PL: Physical limitation; PROMS: Patient reported outcomes; QL: Quality of life score; QoL: Quality of life; SAVR: Surgical aortic valve replacement; SF-36: Short-Form Health Survey-36; TAVI: Transcatheter aortic valve implantation; TAVR: Transcatheter aortic valve replacement.

evaluated by the SF-36 increased from 55 to 66 and mental health increased from 60 to 66 in 4 years[8].

Functional capacity and cardiac surgery

Patients undergoing cardiac surgery are likely to experience complications such as impaired mobility, worsened functional capacity, and decreased muscle strength. Functional status 1 year after cardiac procedures and long-term intensive care stays were significantly lower than the preoperative scores[11]. Despite that, the findings of recent clinical studies indicate improvement of exercise capacity after CABG or valve replacement[31,53-55]. The DASI score showed a 50% improvement in physical function[34], and a prospective study[12] found that the percentage of New York Heart Association class III/IV patients decreased from 59% to 30.3% 10 years post-cardiac surgery (P < 0.013).

Inspiratory muscle training (IMT) improves exercise capacity, lung function, and inspiratory muscle strength. A recent study reported the beneficial effect of IMT on exercise capacity, respiratory muscle strength, inspiratory muscle endurance, QoL, and laboratory biomarkers in patients after CABG[31]. A study of twice-daily IMT in patients from the third postoperative day until 4 weeks after valve replacement found that inspiratory muscle strength and lung function values were restored to pre-operative values, and functional capacity significantly increased[9]. A similar study found improvements in lung function, inspiratory pressure, and functional capacity 6 months after mitral valve replacement surgery[35]. The results of that study agree with the report by Cordeiro *et al*[56] in which, after cardiac surgery, patients underwent respiratory muscle training, conducted twice daily from the ICU discharge until hospital discharge. However, a recent randomized and controlled pilot trial conducted by the same research group[15] found that IMT did not provide greater benefits than usual care for improving functional capacity in patients after CABG. Nonetheless, the study did show that IMT led to a reduction in pulmonary complications and shortened hospital stays.

CR and cardiac surgery

CR and physical activity after cardiac surgery decrease morbidity and frailty and improve QoL and physical and cognitive disorders. CR after coronary artery revascularization is a Class IA recommendation of the ACC/AHA/SCAI guidelines. The evidence supports exercise rehabilitation to decrease hospitalizations and increase functional capacity, exercise tolerance, and HRQoL[57]. However, many patients remain (49.5%) or become (39.0%) physically inactive after cardiac surgery[58]. A CR program includes a number of interventions such as patient assessment, education regarding medical adherence and cardiovascular risk management, dietary recommendations, psychosocial support, behavior modification, personalized exercise training, and physical activity counseling[57,59]. After cardiac surgery, the patient must resume optimal functioning to carry out daily activities and adopt a healthy lifestyle for a lifetime. Therefore, short- and long-term goals are essential components of CR[60]. The program should be prescribed either before hospital discharge or at the initial outpatient visit[57]. In the acute phase[60], rehabilitation includes early mobilization during hospitalization, within the first 24 h[61]. Mobilization includes active-passive range of motion exercises, changing

position, respiratory physiotherapy, neuromuscular electrical stimulation, and virtual reality training[60-63].

After discharge from the hospital, outpatient care and maintenance incorporates supervised progressive exercise that is center- or home-based and performed either face-to-face or in an alternative model, patient education, and behavior modification[64]. The optimal type of exercise, intensity, and duration are tailored to safety and effectiveness criteria[57]. The appropriate dose of exercise is defined by individual tolerance and clinical efficacy, and cardiopulmonary exercise testing combined with echocardiography are used for clinical assessment and risk stratification[30]. Training sessions vary in intensity (50%-95% of peak heart rate, heart rate reserve, or exercise capacity), modality (cycle ergometer, treadmill walking, circuit training, cross-country skiing, and ball games), and duration (20-80 min per session including warm-up and cool-down exercises)[64]. The costs and effectiveness of home- and center-based CR for QoL improvement are comparable[57].

Patients undergoing transcatheter aortic valve intervention or SAVR benefit similarly from CR[38]. In phase II CR, the QoL of CABG patients was found to be significantly correlated with either peak oxygen uptake or functional aerobic impairment by previous studies[65,66]. An early CR exercise program including active range-of-motion exercises from the day following heart valve surgery until hospital discharge improved physical function[67]. Similarly, 3 weeks of bicycle exercise, walking, and strength training combined with education and psychological support begun before discharge increased functional and emotional status after aortic valve replacement[68].

A 36-session outpatient CR program of physical exercise, lifestyle modification, and pharmacotherapy also benefited patients after CABG. The 12-week program improved QoL and exercise tolerance and mitigated cardiac risk factors in 370 patients with diabetes and 942 without diabetes[69]. A prospective study of the QoL of patients before cardiac surgery, 1 month after surgery, and after CR[3] found that patients had a low QoL before surgery and had low scores in all subscales other than social functioning. One month after surgery, the subscale scores had improved but still indicated an unsatisfactory QoL. One year following surgery, almost all subscales were satisfactory. After rehabilitation, there was a considerable improvement in all trajectories of the SF-36, with the highest increase in score for the change in physical pain and the lowest score in the area of physical role functioning.

CONCLUSION

This overview of recently published studies reveals the significance of QoL and functional capacity as key outcome measures for patients after cardiac surgery. After undergoing cardiac surgery, it is recommended that all patients be assessed with standardized assessment tools such as the EQ-5D, SF-36, and DASI to determine their QoL and functional capacity. Most patients significantly improve their physical and mental status capacity. With increasing age, patients are at higher risk of experiencing a deterioration of postoperative QoL and slow functional recovery. Pre-, intra-, and postoperative risk factors should be identified early, prevented, and treated to improve QoL and functional capacity after cardiac surgery. Evidence of the benefits of rehabilitation on improving cardiorespiratory fitness and cardiovascular function are clear and undeniable. Therefore, systematic efforts to implement national guidelines regarding the management of cardiovascular health, high referrals to CR programs, adherence, and compliance comprise an excellent strategy to increase patient participation.

FOOTNOTES

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Observational Study

Sodium-dependent glucose transporter 2 inhibitors effects on myocardial function in patients with type 2 diabetes and asymptomatic heart failure

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Abstract

BACKGROUND

Sodium-dependent glucose transporter 2 inhibitors (SGLT2i) have shown efficacy in reducing heart failure (HF) burden in a very heterogeneous groups of patients, raising doubts about some contemporary assumptions of their mechanism of action. We previously published a prospective observational study that evaluated mechanisms of action of SGLT2i in patients with type 2 diabetes who were in HF stages A and B on dual hypoglycemic therapy. Two groups of patients were included in the study: the ones receiving SGLT2i as an add-on agent to metformin and the others on dipeptidyl peptidase-4 inhibitors as an add-on to metformin due to suboptimal glycemic control.

AIM

To evaluate the outcomes regarding natriuretic peptide, oxidative stress, inflammation, blood pressure, heart rate, cardiac function, and body weight.

METHODS

The study outcomes were examined by dividing each treatment arm into two

subgroups according to baseline parameters of global longitudinal strain (GLS), N-terminal pro-brain natriuretic peptide, myeloperoxidase (MPO), high-sensitivity C-reactive protein (hsCRP), and systolic and diastolic blood pressure. To evaluate the possible predictors of observed changes in the SGLT2i arm during follow-up, a rise in stroke volume index, body mass index (BMI) decrease, and lack of heart rate increase, linear regression analysis was performed.

RESULTS

There was a greater reduction of MPO, hsCRP, GLS, and blood pressure in the groups with higher baseline values of mentioned parameters irrespective of the therapeutic arm after 6 months of follow-up. Significant independent predictors of heart rate decrease were a reduction in early mitral inflow velocity to early diastolic mitral annular velocity at the interventricular septal annulus ratio and BMI, while the predictor of stroke volume index increase was SGLT2i therapy itself.

CONCLUSION

SGLT2i affect body composition, reduce cardiac load, improve diastolic/systolic function, and attenuate the sympathetic response. Glycemic control contributes to the improvement of heart function, blood pressure control, oxidative stress, and reduction in inflammation.

Key Words: Sodium-dependent glucose transporter 2 inhibitors; Dipeptidyl peptidase-4 inhibitors; Type 2 diabetes mellitus; Heart failure; Diabetic cardiomyopathy; Cardiovascular disease

Core Tip: This study evaluated the outcomes regarding natriuretic peptide, oxidative stress, inflammation, blood pressure, heart rate, cardiac function, and body weight derived from our published prospective observational study, which assessed sodium-dependent glucose transporter 2 inhibitors (SGLT2i) mechanisms of action in patients with type 2 diabetes and heart failure (HF) stages A and B on dual oral antidiabetic therapy. Mechanisms underlying favorable SGLT2i effects on HF are related to changes in body composition, reduced cardiac load, better cardiac function, and attenuation of sympathetic response, depending on the HF stage and patients' specific characteristics. Nevertheless, glycemic control itself could contribute to heart function improvement.

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INTRODUCTION

Heart failure (HF), a clinical syndrome defined by its progressive nature, is becoming a growing health problem, carrying a 5-year mortality risk of around 75%[1]. People living with diabetes, one of the largest global public health problem as well, are especially prone to developing cardiovascular disease (or to be specific-macrovascular complication of diabetes) but also diabetic cardiomyopathy, a particular form of cardiomyopathy that develops independently of concomitant macro- and microvascular diabetic complications[2,3]. Indeed, the risk of developing HF in people with diabetes is two- to five-fold greater compared to those without[4]. Sodium-dependent glucose transporters inhibitor (SGLT2i), initially developed for treating hyperglycemia, have become a new panacea in HF therapy since they showed efficacy in reducing cardiovascular risk and HF burden irrespective of the initial HF type (preserved, reduced, or mildly reduced left ventricle ejection fraction) and the presence of established HF at baseline as well as independently of the diabetic status[5-9]. Despite the abundance of new information regarding SGLT2i mechanisms of action, the present literature focuses primarily on patients without diabetes and with advanced HF stages (C and D). Nevertheless, we must be aware that early treatment is important to prevent the progression of asymptomatic HF, especially in patients with type 2 diabetes (T2DM) and diabetic cardiomyopathy where timely treatment could favorably impact the prognosis independently of atherosclerotic cardiovascular disease[10].

Grubić Rotkvić *et al*[11] previously published the design and results from a prospective observational study that evaluated the possible mechanisms of action of SGLT2i in patients with T2DM who were in HF stages A and B and hence at risk of developing symptomatic HF. The study population consisted of two groups of patients with T2DM followed for 6 months: the ones that received SGLT2i as an add-on agent and others on dipeptidyl peptidase-4 inhibitors (DPP-4i) as an add-on to metformin. Here, we examined the study outcomes by further dividing each treatment arm into two subgroups according to the ranking of baseline resting parameters of interest that did not demonstrate significant changes between the treatment groups at the 6 months follow-up in the main analysis (global longitudinal strain [GLS] of the left ventricle, N-terminal pro-brain natriuretic peptide [NT-proBNP], myeloperoxidase [MPO], high sensitivity C-

reactive protein [hsCRP], systolic and diastolic arterial pressure). Furthermore, we evaluated the possible clinical/echocardiographic predictors of the observed changes in the SGLT2i arm: rise in stroke volume index, body mass index (BMI) decrease, and a lack of heart rate increase at 6 months.

MATERIALS AND METHODS

The study design and population with inclusion and exclusion criteria were previously published[11]. Briefly, it was a prospective, observational, non-randomized, two-center study aiming to verify whether SGLT2i impact biomarkers of myocardial stress, inflammation, and oxidative stress (NT-proBNP, hsCRP, MPO, respectively), diastolic heart function, myocardial contractility and structure assessed by echocardiography, in patients with T2DM and HF stages A and B that were already on metformin but due to suboptimal glycemic control needed treatment intensification with a second antidiabetic agent. The choice of therapeutic drug to add was based on patient-related and drug-specific factors and according to the valid international and Croatian guidelines on second-line diabetic therapy at the time the study was conducted[12]. The groups that received SGLT2i as an add-on agent, and for comparison, DPP-4i as an add-on to metformin (due to their presumed neutral effect on the heart except saxagliptin), were followed for 6months. SGLT2i available in our country at that time were: dapagliflozin and empagliflozin, while DPP-4i were the following: sitagliptin, linagliptin, alogliptin, vildagliptin, and saxagliptin (the latter was not used due to a potential increased risk of HF hospitalization). In our study, the patients were taking mostly vildagliptin (90% of patients in the DPP-4i group), and the rest were on sitagliptin, linagliptin, and alogliptin. Among SGLT2i, the most used agent was empagliflozin (81% of patients in the SGLT2i group), while the remaining patients were taking dapagliflozin. The study was conducted at two University hospitals in Zagreb, Croatia, between 2019 and 2022. Inclusion criteria were as follows: the need for an add-on agent (SGLT2i or DPP-4i, saxagliptin excluded) in addition to metformin due to inadequate glycemic control; age ≥ 18 years; willingness to participate in the study; preserved kidney and hepatic function; stable doses of cardioactive drugs such as hypolipemics and antihypertensives if they had them; and stable usual daily physical activities and/or habits. The following exclusion criteria were applied: patients unlikely to comply with study protocol; inability to give informed consent; known atherosclerotic cardiovascular disease; history or symptoms and signs of HF; breastfeeding or pregnancy; acute or chronic inflammatory or autoimmune disease; history of active neoplastic disease within the last 5 years; or use of any other antidiabetic agent besides metformin. Overall, 64 consecutive patients who met the criteria, 32 in each treatment group, underwent blood pressure, heart rate and anthropometric measurements, blood sample analysis, and echocardiography examination according to international recommendations, at baseline, and after 6 months of follow-up. Baseline characteristics of the study population are presented and adapted from Grubić Rotkvić *et al*[11] in Table 1.

Data were statistically processed using SPSS software (version 24.0; IBM SPSS Statistics for Windows; Armonk, NY, United States) under two-sided test conditions with a 5% significance level. Values are presented as the mean ± standard deviation, or the median and interquartile range, for variables with normal and non-normal distribution, respectively. Differences between the two groups were tested using the independent samples *t*-test and a non-parametric substitute for independent samples (Mann-Whitney *U* test) where the conditions for calculating the *t*-test were missing. Differences between initial and follow-up measurements were checked with repeated measures analysis of variance (taking into account potential confounding factors such as the covariates hemoglobin A1c (HbA1c), sex, age, and BMI), with Bonferroni correction for multiple comparisons. A *t*-test for independent samples was used to test the significance of differences in absolute changes in the follow-up period. Additionally, the differences between the two time points were analyzed for certain clinically relevant variables that did not show significant differences in the main analysis (GLS, NT-proBNP, MPO, hsCRP, systolic, and diastolic arterial pressure) by dividing the treatment groups into subgroups according to their initial values. All variables were divided according to their initial median, and a series of two-way tests was performed (analysis of covariance [ANCOVA], covariates: age, sex, BMI, and HbA1c) to test for differences between treatment groups concerning the categorization of patients according to the initial value. Furthermore, whether certain biochemical and echocardiographic parameter of clinical importance predicts the observed changes during time was verified by linear regression analysis. The analysis was performed for a group of variables in which the changes in the main analysis were more pronounced and/or clinically significant such as stroke volume index, BMI, and heart rate. Variables assumed to be related to a particular criterion were entered as potential predictors, as well as HbA1c, BMI, age, and sex (as a dummy variable, binarized) and treatment group (also a dummy variable). Three multivariate regression models for three dependent criteria were developed. The selection of predictors was based on the initial screening of their relationship with the dependent variable and assumed clinical relevance. All variables were entered into the model at the same time (method enter-a procedure for variable selection in which all variables in a block are entered in a single step). A biomedical statistician performed the statistical review of the study.

The ethics committees of the participating institutions approved the protocol, and all patients gave written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

RESULTS

Two-way ANCOVA did not find a statistically significant difference between the two subgroups of patients according to initial NT-proBNP value: subgroups with NT-proBNP more or less than 68 pg/mL (F-ratio (F) (1.52) = 0.422, P = 0.519). There was no significant difference between treatment groups (F (1.52) = 3.032, P = 0.088), nor was there a significant

Table 1 Baseline characteristics of the study population

Characteristics			Group				Total		*P* value
			Metformin + DPP-4i		Metformin + SGLT2i		*n*	(%)	
			n	(%)	*n*	(%)			
Age in yr		≤ 60	12	37.5	19	59.4	31	49.2	0.178
		61-70	13	40.6	7	21.9	20	31.7	
		> 70	7	21.9	6	18.8	13	19.0	
Total			32	100.0	32	100.0	64	100.0	
Sex		Males	18	56.3	18	56.3	36	56.3	0.999
		Females	14	43.8	14	43.8	28	43.8	
Total			32	100.0	32	100.0	64	100.0	
Body mass index in kg/m^2		18.51-24.99	2	6.3			2	3.1	0.005[a]
		25.00-29.99	15	46.9	10	31.3	25	39.1	
		30.00-34.99	14	43.8	11	34.4	25	39.1	
		≥ 35.00	1	3.1	11	34.4	12	18.8	
Total			32	100.0	32	100.0	64	100.0	
Comorbidities	Arterial hypertension		28	87.5	22	68.8	50	78.1	0.066
	Hyperlipidemia		20	62.5	16	50.0	36	56.3	0.337
Drugs	ACEi/ARB		24	75.0	19	59.4	43	67.2	0.178
	Beta-blockers		8	25.0	8	25.0	16	25.0	0.999
	Calcium channel blockers		17	53.1	13	40.6	30	46.9	0.340
	Diuretics		15	46.9	12	37.5	27	42.2	0.470
	Moxonidine		8	25.0	5	15.6	13	20.3	0.378
	Statins		20	62.5	16	50.0	36	56.3	0.337
	Fibrates		1	3.1	2	6.3	3	4.7	0.567

[a]$P < 0.05$.

ACEis: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; DPP-4i: Dipeptidyl peptidase-4 inhibitors; SGLT2i: Sodium-dependent glucose transporters inhibitors.

interaction of two factors (group x initial NT-proBNP group): F (1.52) = 0.469, $P = 0.497$.

A borderline difference in MPO change between the two subgroups according to the initial MPO value (F (1.59) = 3.176, $P = 0.052$) was found. There was a greater reduction in the subgroup with a higher baseline value ≥ 91, 0.8 ng/mL. There was no significant difference between the treatment groups (F (1.59) = 1.797, $P = 0.186$), nor was there a significant interaction of two factors (group x initial MPO group): F(1.59) = 1.036, $P = 0.314$.

There was a significant difference in hsCRP change between the two subgroups according to the initial hsCRP value (F (1.59) = 6.838, $P = 0.012$), namely, a greater reduction in the average value was noticed in the subgroup that had an initial hsCRP ≥ 1.91 mg/L. There was no significant difference between the treatment groups (F (1.59) = 0.784, $P = 0.380$), nor was there a significant interaction between the two factors (group x initial hsCRP group): F (1.59) = 0.194, $P = 0.662$ (Figure 1).

A significant difference in change in systolic pressure between the two subgroups according to the initial systolic pressure value (F (1.60) = 14.917, $P < 0.001$) was found. Systolic pressure decreased more in the subgroup that had an initial systolic pressure higher than 131 mmHg. No significant difference was found between treatment groups (F (1,60) = 0.281, $P = 0.598$); however there was a significant interaction of two factors (group x initial blood pressure group): F (1,60) = 7.867, $P = 0.029$, resulting from the fact that both DPP-4i and SGLT2i lowered systolic pressure in subgroups that had initial pressure > 131 mmHg, but in subgroups with initial pressure ≤ 131 mmHg, systolic pressure increased slightly higher in the SGLT2i group (Figure 2).

There was a statistically significant difference in the change in diastolic pressure between the two subgroups according to the initial diastolic pressure value (F (1.60) = 23.277, $P < 0.0001$). Diastolic pressure decreased more in the subgroup with initial pressure > 80.50 mmHg. No significant difference was found between treatment groups (F (1.60) = 0.423, $P = 0.518$), as well as in the interaction of two factors (group x initial blood pressure group): F (1.61) = 0.227, $P = 0.636$ (Figure 3).

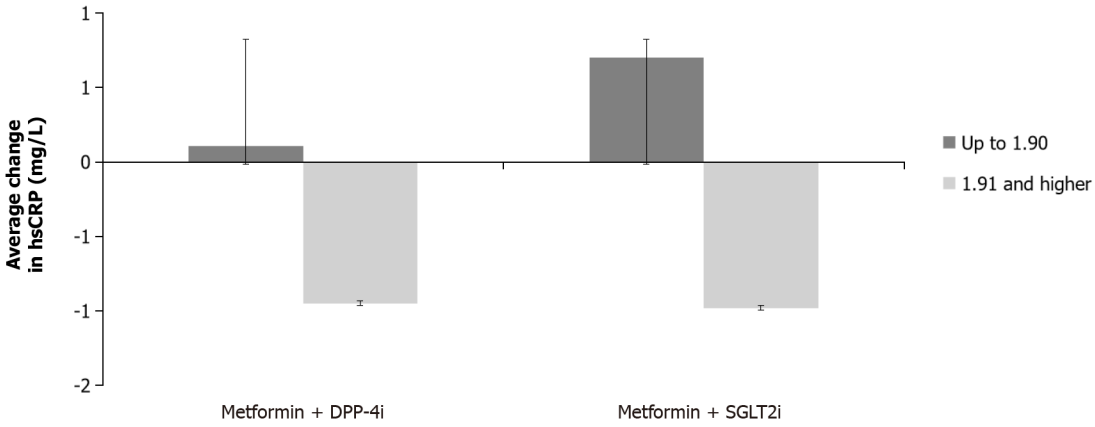

Figure 1 Mean change in high-sensitivity C-reactive protein concerning treatment group and baseline high sensitivity C-reactive protein level. DPP-4i: Dipeptidyl peptidase-4 inhibitors; SGLT2i: hsCRP: High-sensitivity C-reactive protein; Sodium-dependent glucose transporters inhibitors.

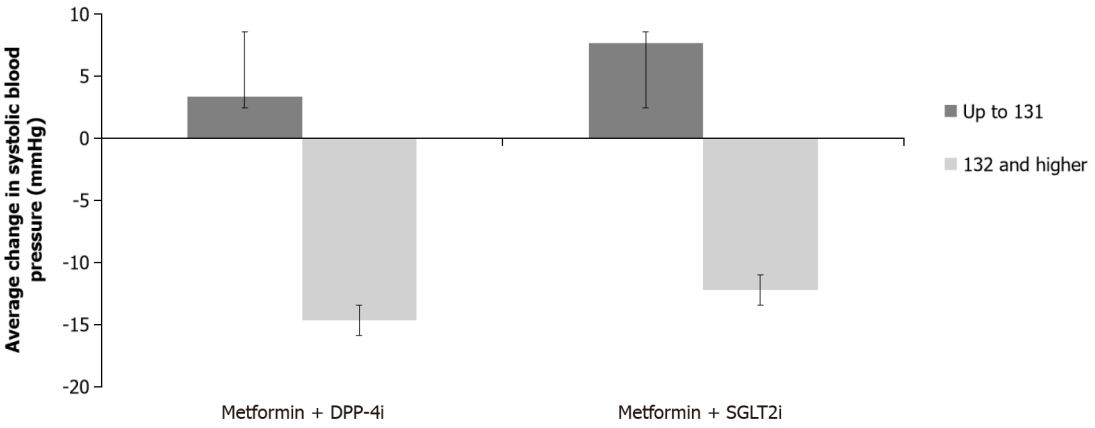

Figure 2 Mean change in systolic blood pressure concerning treatment group and its baseline level. DPP-4i: Dipeptidyl peptidase-4 inhibitors; SGLT2i: Sodium-dependent glucose transporters inhibitors.

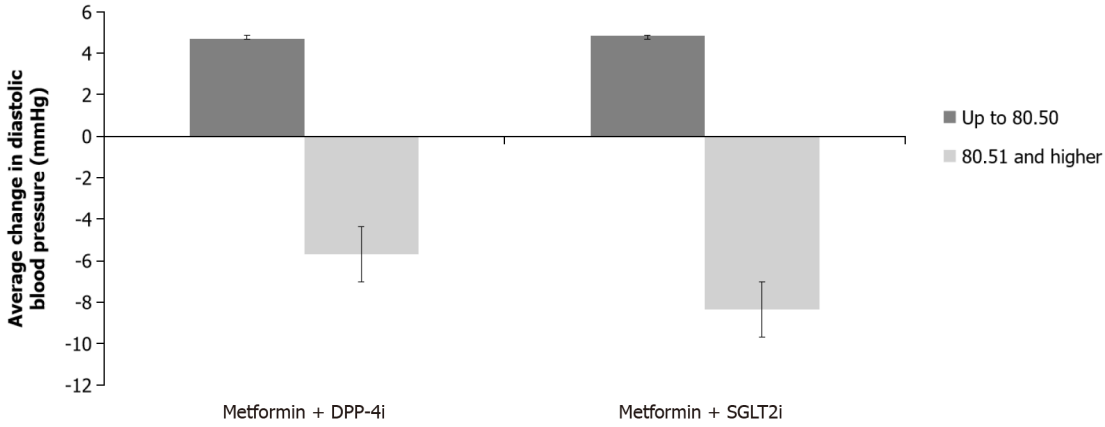

Figure 3 Mean change in diastolic blood pressure concerning treatment group and its baseline level. DPP-4i: Dipeptidyl peptidase-4 inhibitors; SGLT2i: Sodium-dependent glucose transporters inhibitors.

Two-way ANCOVA found a statistically significant difference between the two subgroups of patients according to the initial GLS (F (1.46) = 11.675, $P < 0.001$). In the subgroup where the initial GLS was > -17.84% the change was greater (resulting in more negative values hence better GLS). No significant difference was found between treatment groups (F (1.46) = 0.536, $P = 0.468$), nor was there a significant interaction of two factors (group x initial GLS group): F (1,46) = 0.270, $P = 0.606$ (Figure 4).

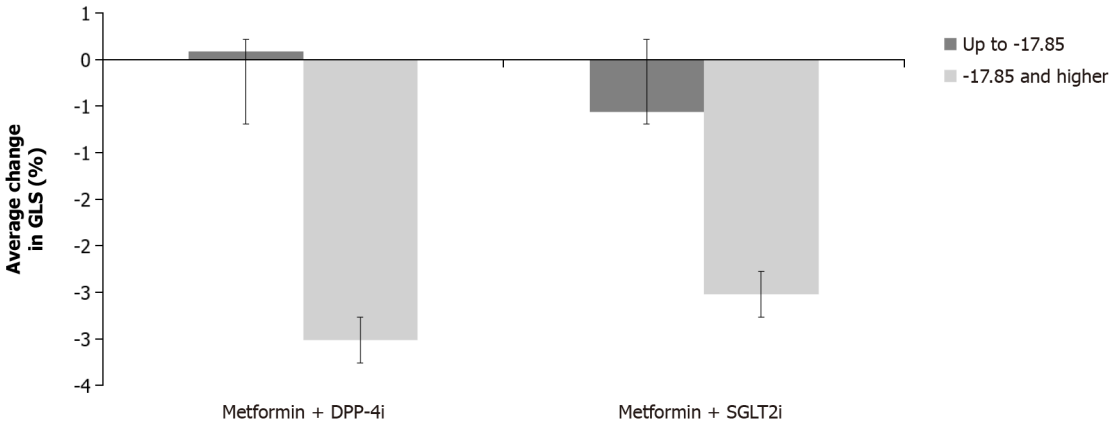

Figure 4 Mean change in global longitudinal strain concerning treatment group and baseline global longitudinal strain level. GLS: Global longitudinal strain; DPP-4i: Dipeptidyl peptidase-4 inhibitors; SGLT2i: Sodium-dependent glucose transporters inhibitors.

In the regression analysis model with an increase in stroke volume index as a criterion, the variables hemoglobin, erythrocytes, hematocrit, BMI, sex, age, HbA1c, and therapeutic group as potential predictors were entered. The model explained 23% of the variance (adjusted R^2 = 0.231, F = 2.162, P = 0.071): SGLT2i therapy was the only significant independent predictor (beta-coefficient = 0.480, 95% confidence interval [CI]: 0.129-16.653, P = 0.047).

In the regression analysis model with BMI reduction as a criterion and potential predictors (relative wall thickness, low-density lipoprotein, triglycerides, high-density lipoprotein, HbA1c, age, sex, therapeutic group), the model explained 9% of the variance (adjusted R^2 = 0.087, F = 1.349, P = 265) and there were no significant predictors.

Another regression analysis for the reduction of heart rate as a criterion was performed with the following possible predictors: early diastolic mitral annular velocity at the interventricular septal annulus (E' septal), early mitral inflow velocity to early diastolic mitral annular velocity at the interventricular septal annulus ratio (E/E'), early mitral inflow velocity to atrial filling velocity ratio (E/A), early mitral inflow velocity (E-wave), GLS, left ventricular ejection fraction, tricuspid annular plane systolic excursion (TAPSE), as well as BMI, HbA1c, age, sex, and therapeutic group. For the reduction of heart rate, the model explains 16% of the variance (adjusted R^2 = 0.165, F = 1.708, P = 0.113). Significant independent predictors of heart rate reduction were the E/E' ratio (beta-coefficient = 0.728, 95%CI: 0.038-4.097, P = 0.047) and BMI (beta-coefficient = 3.450, 95%CI: 0.935-3.639, P = 0.002).

DISCUSSION

This subanalysis, where the patients were categorized according to the baseline measurements into those with higher and lower initial values (according to the obtained median), showed that there was no statistically significant difference between the two groups of patients concerning the initial NT-proBNP, which was consistent with our previous finding and could mean that volume homeostasis is not that significant in this particular patient population. Even in the literature, there have been inconsistent findings concerning the effect of SGLT2i on natriuretic peptides in different groups of patients regarding diabetes or HF status, ranging from slightly increasing and decreasing NT-proBNP to no effect at all[13-16]. In the EMPEROR-Reduced trial, SGLT2i empagliflozin showed a similar effect on reducing the risk of adverse cardiovascular outcomes across different NT-proBNP quartiles[17]. It could be hypothesized that SGLT2i enhances the beneficial physiological action of natriuretic peptides by the competition for the same target since there are reports from experimental studies that atrial natriuretic peptide inhibits renal SGLT2 activity, which could play a role in postponing the symptomatic phase of ventricular dysfunction in people with diabetes as in our specific group of patients with asymptomatic HF A and B stages[11,18].

Regarding MPO, there was a difference of marginal significance in the change of MPO values between the two subgroups according to baseline MPO. A greater reduction was noted in the group with a higher baseline value (≥ 91.08 ng/mL) without a significant difference between the treatment groups. There was also a significant difference in the change of hsCRP between the two subgroups categorized according to baseline hsCRP level. The average value decreased more in the group with initial hsCRP ≥ 1.91 mg/L. Again, no significant difference was found between therapeutic groups or the interaction of two factors. Previously, without categorizing the patients according to baseline MPO and hsCRP values, we did not find any differences during follow-up which could be interpreted in the time context since the effect on systemic inflammation and oxidative stress may only become apparent after a period longer than 6 months, especially in patients who have not yet developed chronic complications of diabetes[19]. However, it should not be ignored that in the categories of patients with higher hsCRP and MPO, the values were lowered during the follow-up period of 6 months in both treatment groups, stressing the potential effect of better glycemic control influencing oxidative stress and inflammation. Both oxidative stress and inflammation are closely related to the development of diabetic cardiomyopathy[2]. Comparing the previously mentioned average values of hsCRP and MPO from our study with literature data, borderline hsCRP values of low, average, and high cardiovascular risk were < 1.0 mg/L, 1.0-3.0 mg/L, and > 3.0 mg/L, respectively, whereas in the study by Nita *et al*[20], where the effect of fenofibrate was studied on basal

MPO values in patients with T2DM on metformin monotherapy but with good glucoregulation, the median MPO was 55.0 (38.5-85.3) ng/mL[20,21]. Our population had a hsCRP median that would be classified as intermediate risk. The MPO was higher than in the study of Nita *et al*[20], perhaps due to inadequate glycemic control in our population when entering the study.

When the change in systolic pressure was analyzed concerning the therapeutic group and the division into subgroups according to the initial systolic pressure, there was a significant difference in the change in systolic pressure over time with a significant interaction of the two factors: The systolic pressure decreased with both DPP-4i and SGLT2i in subgroups that had initial pressure > 131 mmHg, while in subgroups with initial pressure ≤ 131 mmHg, systolic pressure increased, slightly more in the group on SGLT2i. There was also a statistically significant difference in the change of the diastolic pressure between the two subgroups, it decreased more in the group with initial pressure > 80.50 mmHg. Previous studies have mostly shown that SGLT2i lowers systolic blood pressure, and according to a recent meta-analysis, there was no reduction in diastolic blood pressure. However, the data are still not uniform, for example in the EMPEROR-Preserved and EMPEROR-Reduced randomized trials with empagliflozin in patients with reduced and preserved left ventricular ejection fraction, marginal changes were found between the groups treated with empagliflozin compared to placebo, so it was concluded that empagliflozin is effective in HF favorable outcomes independently of its antihypertensive effect. Moreover, similar to our study, there was an overall increase in systolic blood pressure at low baseline values (< 110 mmHg) as well as a small drop in systolic blood pressure at higher baseline values (> 130 mmHg) in those trials. The effect of empagliflozin was maintained at systolic blood pressure even < 110 mmHg, without causing any harm which is of clinical relevance since physicians often hesitate to initiate treatment due to the fear of over-lowering the blood pressure[7,22,23]. Reports of arterial pressure reduction also exist for DPP-4i[24]. Taken together, both drugs could account for a beneficial effect on blood pressure which could also be due to better glycemic control in this specific population.

Furthermore, when the patients were categorized depending on the initial GLS value, there was a statistically significant change in patients with GLS > -17.84% (those with subclinical contractile dysfunction since normal values are considered to be ≤ -18%). In this category of patients, regardless of the applied therapy, there was an improvement in the value of the longitudinal cardiac deformation. GLS of the left ventricle measured by speckle-tracking echocardiography is a more sensitive technique to assess left ventricular contractility and compared to ejection fraction, is less load-dependent. Hence, it could be more reliable in earlier detection of subclinical left ventricle dysfunction[16]. In the study of Nesti *et al* [16] who also conducted a sub-analysis of the subgroups with higher and lower baseline GLS among patients followed for 6 months on empagliflozin and sitagliptin therapy, the group with higher GLS showed no change during the study. In contrast, the patients with lower baseline GLS experienced an improvement in left ventricle contractility after 1 month of therapy with empagliflozin followed by a further improvement at 6 months. In the sitagliptin arm, there was no such change after 1 month, but a mild improvement was noticed at 6 months.

In the regression analysis model with BMI reduction as a criterion and potential predictors (relative wall thickness, low-density lipoprotein, triglycerides, high-density lipoprotein, HbA1c, age, sex, therapeutic group), no significant predictors were determined.

A regression analysis was performed for the increase in stroke volume index as a criterion, and the biochemical variables hemoglobin, erythrocytes, hematocrit and BMI, sex, age, HbA1c, and therapeutic group were entered as potential predictors. Therapy with SGLT2i proved to be the only significant independent predictor of an increase in stroke volume index. The possible explanation for the rise in stroke volume index observed in our main analysis could be the decrease in systemic vascular resistance (afterload), which could be mediated through small increases in hematocrit (also linked to SGLT2i and confirmed in our study as well) that consequently increases blood viscosity and reduce vascular resistance (creating an increase in friction in the area of the microvasculature and stimulating vasoactive substances such as nitric oxide)[11,25]. Moreover, reducing afterload facilitates ventricular emptying and leads to an increase in stroke volume while diminishing myocardial oxygen demand which is more energy efficient.

Due to the clinical importance of possible predictors of heart rate reduction (or at least the absence of an increase which would be expected due to diuretic properties of SGLT2i), a regression analysis was performed with the following possible predictors: E' septal, E/E', E/A, E-wave (parameters of diastolic function) and GLS, left ventricular ejection fraction, TAPSE (systolic function parameters), as well as BMI, HbA1c, age, sex, and therapeutic group. The analysis showed that the lowering of BMI and E/E' in our study contributes to heart rate reduction during SGLT2i therapy. It is known that both obesity and diastolic dysfunction, potential targets of SGLT2 inhibition, are associated with increased sympathetic activity[11,26,27].

CONCLUSION

As the results of these subanalyses showed effects in both therapeutic groups after stratification into more specific subgroups, it is certainly possible that the improvement of glycemia itself contributed to the improvement of heart function emphasizing that patients with T2DM encompass a different category of patients with potentially distinct pathophysiological mechanisms involved in the process of the failing heart. However, we also need to account for the limitations of this study being a subanalysis with a rather small sample size (hence possible non-trustable null findings that showed no significant differences between the two therapeutic groups in the sub-analyses) and potentially lasting for a too short period for some effects to be seen. Furthermore, there is a possibility of differences between individual agents within the same class as we included the DPP-4i and SGLT2i that were available in our country. Due to a relatively small sample size, we could not investigate extensive multivariable associations with outcomes. To adjust for the potential

confounding effect of adiposity, the gold standard would be to measure abdominal visceral adipose tissue using magnetic resonance imaging and/or computed tomography instead of a BMI, but this is an expensive approach and is not always available in routine clinical practice[28]. In addition, there are also conflicting results concerning the possible DPP-4i antioxidant and anti-inflammatory effects, which in experimental studies suggested cardiovascular efficiency but were not consistently proven in human studies[29,30]. Nevertheless, it seems that our comparators are not completely neutral on cardiac function. However, mechanisms underlying the benefits of SGLT2i and their undoubtedly favorable effects in HF are multifactorial-connected to rapid changes in body composition, reduced cardiac load, improvement in diastolic and systolic parameters, and probably attenuation of sympathetic response, while depending on the stage of HF and patients' specific characteristic as well as comorbidities. Additional studies are needed to enlighten the mechanisms underlying this complex cardiometabolic interplay.

FOOTNOTES

Author contributions: Grubić Rotkvić P designed the study, performed the research, and wrote the original draft; Rotkvić L and Đuzel Čokljat A, analyzed the data, and reviewed and edited the manuscript; Cigrovski Berković M designed the study, performed the research, and supervised the study; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

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Nomogram predicting the cardiovascular disease mortality for older patients with colorectal cancer: A real-world population-based study

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Abstract

BACKGROUND

Cardio-oncology has received increasing attention especially among older patients with colorectal cancer (CRC). Cardiovascular disease (CVD)-specific mortality is the second-most frequent cause of death. The risk factors for CVD-specific mortality among older patients with CRC are still poorly understood.

AIM

To identify the prognostic factors and construct a nomogram-based model to predict the CVD-specific mortality among older patients with CRC.

METHODS

The data on older patients diagnosed with CRC were retrieved from The Surveillance, Epidemiology, and End Results database from 2004 to 2015. The prognostic factors and a nomogram-based model predicting the CVD-specific mortality were assessed using least absolute shrinkage and selection operator and Cox regression.

RESULTS

A total of 141251 eligible patients with CRC were enrolled, of which 41459 patients died of CRC and 12651 patients died of CVD. The age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy were independent prognostic factors associated with CVD-specific mortality among older patients with CRC. We used these variables to develop a model to predict CVD-specific mortality. The calibration curves for CVD-specific mortality probabilities showed that the model was in good agreement with actual observations. The C-index value of the model in the training cohort and testing cohort for predicting CVD-

specific mortality was 0.728 and 0.734, respectively.

CONCLUSION
The proposed nomogram-based model for CVD-specific mortality can be used for accurate prognostic prediction among older patients with CRC. This model is a potentially useful tool for clinicians to identify high-risk patients and develop personalized treatment plans.

Key Words: Older patients; Colorectal cancer; Cardio-oncology; Nomogram; Outcome

Core Tip: For older patients with colorectal cancer (CRC), cardiovascular disease (CVD)-specific mortality is the second-most frequent cause of death. Herein, we analyzed data from the Surveillance, Epidemiology, and End Results program. The age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy were independent prognostic factors associated with CVD-specific mortality among older patients with CRC. Six variables were independent prognostic factors. Subsequently, we proposed a nomogram-based model of the CVD-specific mortality that could be used for accurate prognostic prediction of older patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the third-most deadly cancer worldwide. In 2020, there were 1.9 million new CRC cases[1,2]. Moreover, the incidence rates of CRC have been steadily increasing; the projected increase by 2035 is 2.5 million[2,3]. Cancer-specific mortality is known to be the most common cause for CRC patients[1,3]. With improved treatment options such as endoscopy, surgical local excision, radiotherapy, systemic therapy, chemotherapy, targeted therapy, immunotherapy[1], altered CRC risk factor patterns, and screening, the CRC mortality rates have declined[4]. Thus, the non-cancer causes of death among CRC patients have increased with increasing survival time. Many researchers have been increasingly concerned regarding non-cancer deaths, especially due to cardiovascular disease (CVD)[5-8]. Cardio-oncology has developed as a relatively new discipline and received increasing attention in clinical treatment. Baraghoshi *et al*[9] showed CRC survivors had almost double the risk of CVD than the general population. Among older patients with CRC, deaths due to cancer and CVD-specific factors were the first and second-most frequent cause of deaths, respectively[8,10].

Therefore, risk factors for cancer-specific mortality and CVD-specific mortality among older patients with CRC merits further analysis. Until now, the risk factors and cardio-oncological factors in older patients with CRC have been poorly understood. Furthermore, there is no predictive model yet that can estimate the CVD risk in older patients with CRC. In this study, we characterized the risk factors for cancer-specific mortality and CVD-specific mortality and established a risk predictive model for CVD-specific mortality, aiming to provide a contemporary and valuable resource for cardiologists and oncologists in their follow-up care of older patients with CRC.

MATERIALS AND METHODS

Patient selection

In this retrospective study, we used data from The Surveillance, Epidemiology, and End Result (SEER) program which is a public tumor registry that covers 34.6% of the US population with cancer.

In total, the clinical data of patients diagnosed with CRC in the SEER program from January 1, 2004 to December 31, 2015 were retrospectively included in this study. All patients aged > 60 years with complete follow-up data and positive malignant histological examination were included. Patients whose clinicopathological information was incomplete were excluded. To further decrease the potential bias, we also excluded patients with < 30 days of follow-up and patients with more than one lifetime history of cancer. Finally, 141251 patients were enrolled in the study (Figure 1).

This observational study used de-identified and publicly available data from the SEER registry and thus did not require formal consent or institutional review board approval. This study was conducted in accordance with the tenets of the Helsinki Declaration.

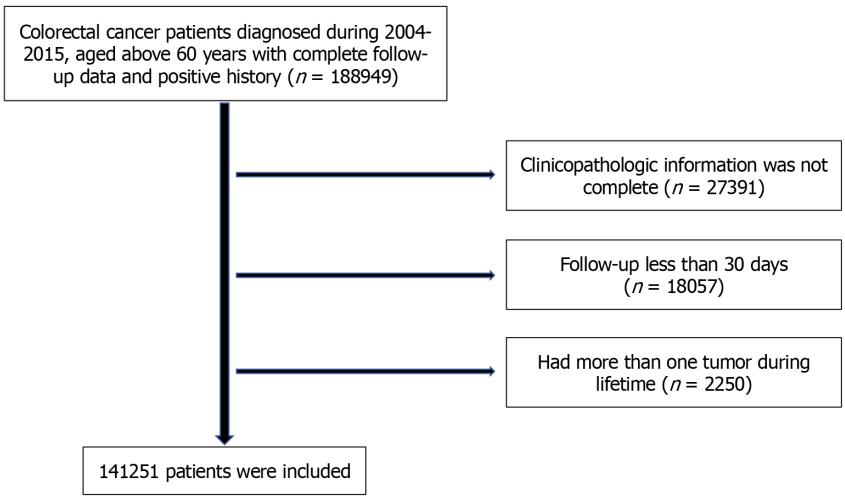

Figure 1 Cohort selection criteria.

Information collection

We collected the basic information of patients, namely age at diagnosis; sex; marital status (single, married, or others); race (White, Black, or others); year of diagnosis; insurance status; primary site (right half colon, left half colon, or rectum); TNM stage; histological grade (well, moderate, poorly, or undifferentiated); histology type (adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma, or others); surgery; radiotherapy; and chemotherapy.

The cause of death classification was recorded from the variable "COD to site recode" in the SEER database. Cancer-specific mortality was defined by the cause of death recorded as CRC. We considered deaths due to heart disease, atherosclerosis, aortic aneurysm and dissection, cerebrovascular disease, hypertension without heart disease, and the diseases of arteries, arterioles, and capillaries as CVD-specific mortality.

Statistical analysis

Univariate and multivariate Cox regression analyses were used to determine the survival risk factors of cancer-specific mortality and CVD-specific mortality in the training cohort. Least absolute shrinkage and selection operator (LASSO) method is a commonly used method for regression with high-dimensional predictors[11]. The LASSO Cox regression model was used to select the most valuable prognostic variables of all CRC and CVD-specific mortality in our study. We constructed the nomogram of CVD-specific mortality according to the LASSO results.

The C-index, calibration curves, and prognostic decision curve analysis (DCA) were created to assess the predictive accuracy and discriminative ability of the nomogram-based model in the training and testing cohorts. R software (version 3.6.1) was used for statistical analysis. $P < 0.05$ was considered to indicate statistically significant differences.

RESULTS

Patient characteristics

A total of 141251 patients with CRC (48.7% male and 51.3% female) were included in this study. The proportion of patients aged 60-69 years was 38.2%, that of patients aged 70-79 years was 34.1%, and that of patients aged ≥ 80 years was 27.7%. In the entire cohort, 41459 patients died of CRC, 12651 patients died of CVD, 73035 patients were alive, and 14106 patients died of other causes. The clinicopathologic characteristics of patients with CRC are summarized in Table 1.

Analysis on the cancer-specific mortality and CVD-specific mortality

Patients were randomly divided into a training cohort (98876 patients) and a test cohort (42375 patients) in a ratio of 7:3 based on the "caret" package on the outcome of "dead." Univariate analysis on the cancer-specific mortality and CVD-specific mortality was performed in the training cohort.

As shown in Table 2, univariate analysis revealed that age was both associated with cancer-specific mortality and CVD-specific mortality. The risk of cancer-specific mortality in patients aged ≥ 80 years was 1.63-times that of patients aged 60-69 years, while the risk of CVD-specific mortality in patients aged ≥ 80 years was 7.31-times that of patients aged 60-69 years. TNM stage was positively associated with cancer-specific mortality. However, the TNM stage was negatively associated with CVD-specific mortality, and the risk of CVD-specific mortality in TNM stage IV was 0.73-times that of TNM stage I. Absence of chemotherapy was associated with cancer-specific mortality, but presence of chemotherapy was associated with CVD-specific mortality.

On multivariate analysis, we found that the age at diagnosis (≥ 80 years *vs* 60-69, HR: 6.43;70-79 *vs* 60-69, HR: 2.44); sex (male *vs* female, HR: 1.58); marital status (married *vs* single, HR: 0.68); year of diagnosis (2008-2011 *vs* 2004-2007, HR: 0.89; 2012-2015 *vs* 2004-2007, HR: 0.79); surgery (no *vs* yes, HR: 2.07); and chemotherapy (no *vs* yes, HR: 0.51) was associated

Table 1 Clinicopathologic characteristics of patients with different outcomes, *n* (%)

Variables	Cancer-specific mortality (*n* = 41459)	CVD-specific mortality (*n* = 12651)	Others-specific mortality (*n* = 14106)	Survivors (*n* = 73035)	Total (*n* = 141251)
Age at diagnosis (years)					
60-69	14188 (34.2)	1911 (15.1)	2750 (19.5)	35112 (48.1)	53961 (38.2)
70-79	13969 (33.7)	3971 (31.4)	4895 (34.7)	25384 (34.8)	48219 (34.1)
≥ 80	13302 (32.1)	6769 (53.5)	6461 (45.8)	12539 (17.1)	39071 (27.7)
Sex					
Female	21112 (50.9)	6395 (50.5)	7294 (51.7)	37631 (51.5)	72432 (51.3)
Male	20347 (49.1)	6256 (49.5)	6812 (48.3)	35404 (48.5)	68819 (48.7)
Marital status					
Single	4908 (11.8)	1296 (10.2)	1431 (10.1)	7802 (10.7)	15437 (10.9)
Married	19950 (48.1)	5414 (42.8)	6312 (44.7)	41601 (57)	73277 (51.9)
Others	16601 (40.1)	5941 (47)	6363 (45.2)	23632 (32.3)	52537 (37.2)
Race					
White	33337 (80.4)	10670 (84.3)	11818 (83.8)	58562 (80.2)	114387 (81)
Black	4928 (11.9)	1232 (9.8)	1318 (9.3)	7158 (9.8)	14636 (10.4)
Others	3197 (7.7)	749 (5.9)	970 (6.9)	7315 (10)	12228 (8.6)
Year of diagnosis					
2004-2007	16825 (40.6)	6651 (52.6)	7135 (50.6)	16055 (22)	46666 (33)
2008-2011	14971 (36.1)	4215 (33.3)	4873 (34.5)	23245 (31.8)	47304 (33.5)
2011-2016	9663 (23.3)	1785 (14.1)	2098 (14.9)	33735 (46.2)	47281 (33.5)
Insurance status					
Insured	27713 (66.8)	7290 (57.6)	8303 (58.9)	59691 (81.7)	102997 (72.9)
Uninsured	576 (1.4)	45 (0.4)	78 (0.6)	1030 (1.4)	1729 (1.2)
Unknown	13170 (31.8)	5316 (42)	5725 (40.5)	12314 (16.9)	36525 (25.9)
Primary site					
Right half colon	20201 (48.7)	6787 (53.6)	7596 (53.8)	35512 (48.6)	20096 (49.6)
Left half colon	10320 (24.9)	3254 (25.7)	3530 (25)	19442 (26.6)	36546 (25.9)
Rectum	10938 (26.4)	2610 (20.6)	2980 (21.2)	18081 (24.8)	34609 (24.5)
TNM stage					
I	3391 (8.2)	4101 (32.4)	4414 (31.3)	24426 (33.4)	36332 (25.7)
II	7956 (19.2)	4755 (37.6)	5207 (36.9)	25190 (34.5)	43108 (30.5)
III	14313 (34.5)	3216 (25.4)	3657 (25.9)	20502 (28.1)	41688 (29.5)
IV	15799 (38.1)	579 (4.6)	828 (5.9)	2917 (4)	20123 (14.3)
Grade					
Well	2399 (5.8)	1314 (10.4)	1459 (10.3)	8479 (11.6)	13651 (9.7)
Moderate	26863 (64.8)	9080 (71.8)	10068 (71.4)	53387 (73.1)	99398 (70.4)
Poorly	10709 (25.8)	2043 (16.1)	2297 (16.3)	9734 (13.3)	24783 (17.5)
Undifferentiated	1488 (3.6)	214 (1.7)	282 (2)	1435 (2)	3419 (2.4)
Histology					
Adenocarcinoma	32932 (79.4)	9709 (76.7)	10920 (77.4)	56050 (76.7)	109611 (77.6)
Mucinous adenocarcinoma and	4075 (9.8)	1073 (8.5)	112 (7.9)	5174 (7.1)	11434 (8.1)

signet-ring cell carcinoma					
Others	4452 (10.8)	1869 (14.8)	2074 (14.7)	11811 (16.2)	20206 (14.3)
Surgery					
Yes	36485 (88)	12112 (95.7)	13507 (95.8)	71367 (97.7)	133471 (94.5)
No	4974 (12)	539 (4.3)	599 (4.2)	1668 (2.3)	7780 (5.5)
Radiotherapy					
Yes	6094 (14.7)	929 (7.3)	1202 (8.5)	9064 (12.4)	17289 (12.2)
No	35365 (85.3)	11722 (92.7)	12769 (91.5)	63971 (87.6)	123962 (87.8)
Chemotherapy					
Yes	19038 (45.9)	2036 (16.1)	2593 (18.4)	24410 (33.4)	48077 (34)
No	22421 (54.1)	10615 (83.9)	11513 (81.6)	48625 (66.6)	93174 (66)

CVD: Cardiovascular disease.

with CVD-specific mortality (Table 2).

Prognostic nomogram-based model construction

We performed LASSO regression analysis to reduce the risk of over-fitting of our model by compressing the partial factorial regression coefficient to zero[12]. After primary filtration, we used penalty parameter tuning performed *via* 10-fold cross-validation to further narrow the variables, which requires the selected variables to appear more than 900 times in a total of 1000 times 10-fold cross-validation repetitions (Figure 2).

Finally, six variables-age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy-were selected to construct the nomogram-based model, which was used to estimate the 3-year and 5-year CVD-specific mortality (Figure 3).

Validating the nomogram-based model

In the training cohort, the C-index of the nomogram for predicting CVD-specific mortality was 0.728 (95%CI: 0.722-0.734), indicating good discrimination. Figure 4A and B show a corrected graph of the prediction accuracy of the nomogram, which shows good consistency between the actual and predicted 3- and 5-year CVD-specific mortality, with a slope of nearly 45°.

Similarly, in the testing cohort, the C-index of the nomogram for CVD-specific mortality was 0.734 (95%CI: 0.725-0.743). Figure 4C and D show the corrected graph of the prediction accuracy of the nomogram, which showed good consistency between the actual and predicted 3- and 5-year cardiovascular mortality rates, with a slope of nearly 45°.

The DCA was plotted to evaluate how clinical benefits affected patients (Figure 5). According to the DCA, our nomogram had a positive net benefit in the training and testing cohorts, with a wide threshold probability range.

DISCUSSION

According to previous studies, older patients with CRC had a significantly higher risk of CVD morbidity and CVD-specific mortality than the general population[5]. Researchers have analyzed various causes of death in patients with different types of cancer and have emphasized that CVD was the most prevalent cause of non-cancer death in patients with cancer[13,14]. In recent years, a new international discipline called cardio-oncology has emerged that integrates cardiology and oncology organically and is receiving extensive attention. Cardio-oncology as a new discipline has now become a research hotspot. In a Canadian study, researchers found that CVD was the leading non-cancer cause of death among older patients with CRC[15]. Our findings were consistent with this Canadian study. In our study, we focused on the cardio-oncological health of older patients with CRC and found that the CVD-specific mortality was 8.96% among older patients with CRC, the second-leading cause of death, after CRC-specific mortality (29.35%). Therefore, it is very important to explore the prognostic factors of CVD-specific mortality in older patients with CRC.

To our best knowledge, the prognostic factors of CVD-specific mortality for older patients with CRC have not yet been completely elucidated, there is no constructed nomogram model for CVD-specific mortality in older patients with CRC. Therefore, our study focused on identifying the prognostic risk factors for CVD-specific mortality among older patients with CRC. In this study, we performed LASSO regression analysis to reduce the risk of over-fitting the model and suggested that the age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy were the key prognostic factors associated with CVD-specific mortality among older patients with CRC. We synthesized a variety of analysis methods to construct a nomogram-based prognostic evaluation model with these six key prognostic factors, and validated the prognostic model with a testing cohort. By using comprehensive analysis and further verification, we found good predictive effect and high reliability. To our knowledge, this is the largest contemporary cohort of CVD-specific

Table 2 Competing risk analysis on the cancer-specific mortality and cardiovascular mortality

Variables	Univariate analysis (cancer-specific mortality)			Univariate analysis (CVD-specific mortality)			Multivariate analysis (cancer-specific mortality)			Multivariate analysis (CVD-specific mortality)		
	HR	95%CI	*P* value	HR	95%CI	*P* value	HR	95%CI	*P* value	HR	95%CI	*P* value
Age at diagnosis (years)												
60-69	Reference			Reference			Reference			Reference		
70-79	1.17	1.14-1.2	< 0.001	2.52	2.36-2.69	< 0.001	1.34	1.3-1.37	< 0.001	2.44	2.29-2.61	< 0.001
≥ 80	1.63	1.58-1.67	< 0.001	7.31	6.88-7.77	< 0.001	1.94	1.88-2	< 0.001	6.43	6.02-6.85	< 0.001
Sex												
Female	Reference						Reference			Reference		
Male	1.03	1.1-1.05	< 0.01	1.07	1.02-1.11	< 0.01	1.16	1.13-1.19	< 0.001	1.58	1.51-1.65	< 0.001
Marital status												
Single	Reference			Reference			Reference			Reference		
Married	0.77	0.74-0.80	< 0.001	0.72	0.67-0.77	< 0.001	0.83	0.80-0.86	< 0.001	0.68	0.63-0.73	< 0.001
Others	0.98	0.94-1.02	0.31	1.28	1.19-1.38	< 0.001	0.98	0.94-1.01	0.21	0.93	0.87-1.00	0.06
Race												
Black	Reference			Reference			Reference			Reference		
White	0.82	0.79-0.85	< 0.001	1.05	0.98-1.12	0.2	0.84	0.81-0.88	< 0.001	0.89	0.83-0.96	< 0.001
Others	0.71	0.68-0.75	< 0.001	0.66	0.50-0.74	< 0.001	0.73	0.69-0.77	< 0.001	0.63	0.57-0.71	< 0.001
Year of diagnosis												
2004-2007	Reference			Reference			Reference			Reference		
2008-2011	0.92	0.9-0.95	< 0.001	0.86	0.82-0.91	< 0.001	0.89	0.87-0.91	< 0.001	0.89	0.85-0.94	< 0.001
2012-2015	0.85	0.83-0.88	< 0.001	0.73	0.68-0.78	< 0.001	0.82	0.8-0.85	< 0.001	0.79	0.74-0.85	< 0.001
Primary site												
Right half colon	Reference			Reference			Reference			Reference		
Left half colon	0.93	0.9-0.95	< 0.001	0.84	0.80-0.89	< 0.001	0.99	0.96-1.02	0.39	1.02	0.97-1.07	0.44
Rectum	1.07	1.04-1.1	< 0.001	0.76	0.72-0.80	< 0.001	1.08	1.04-1.12	< 0.001	1.06	0.99-1.13	0.08
TNM stage												

I	Reference			Reference			Reference			Reference		
II	2.09	1.99-2.19	< 0.001	1.05	1.00-1.11	0.05	1.39	1.29-1.49	< 0.001	1.03	0.98-1.09	0.26
III	4.39	4.19-4.59	< 0.001	0.86	0.81-0.90	< 0.001	2.46	2.28-2.65	< 0.001	0.78	0.63-0.98	0.04
IV	18.42	17.61-19.27	< 0.001	0.73	0.65-0.81	< 0.001	9.26	8.61-9.95	< 0.001	0.87	0.72-1.06	0.17
Grade												
Well	Reference			Reference			Reference			Reference		
Moderate	1.64	1.56-1.72	< 0.001	1.05	0.98-1.13	0.14	1.26	1.2-1.33	< 0.001	1.05	0.99-1.13	0.15
Poorly	3.11	2.95-3.28	< 0.001	1.14	1.05-1.24	< 0.001	1.65	1.56-1.74	< 0.001	1.08	0.98-1.13	0.07
Undifferentiated	3.48	3.22-3.76	< 0.001	1.11	0.93-1.31	0.25	1.81	1.68-1.96	< 0.001	1.11	0.93-1.32	0.26
Histology												
Adenocarcinoma	Reference			Reference			Reference			Reference		
Mucinous adenocarcinoma and signet-ring cell carcinoma	1.26	1.21-1.31	< 0.001	1.14	1.06-1.23	< 0.001	1.05	1.01-1.09	0.01	1.13	1.05-1.22	< 0.01
Others	0.71	0.68-0.74	< 0.001	1	0.94-1.06	0.95	1.01	0.97-1.04	0.77	1.01	0.95-1.07	0.77
Surgery												
Yes	Reference			Reference			Reference			Reference		
No	4.24	4.09-4.4	< 0.001	1.74	1.57-1.94	< 0.001	3.46	3.32-3.62	< 0.001	2.07	1.86-2.32	< 0.001
Radiotherapy												
Yes	Reference			Reference			Reference			Reference		
No	1.22	1.18-1.26	< 0.001	0.57	0.52-0.61	< 0.001	1.17	1.12-1.22	< 0.001	0.99	0.89-1.10	0.9
Chemotherapy												
Yes	Reference			Reference			Reference			Reference		
No	1.66	1.62-1.7	< 0.001	0.39	0.37-0.41	< 0.001	1.66	1.64-1.68	< 0.001	0.51	0.47-0.55	< 0.001

CVD: Cardiovascular disease.

mortality and construction of nomogram-based prognostic evaluation model for older patients with CRC.

Our results indicated that the risk of CRC-specific mortality and CVD-specific mortality were both negatively associated with age at diagnosis. Previous studies have reported that patients with cancer perpetually have a higher risk of dying from CVD than the general population in the United States, and the incidence of any CVD increased with age[16, 17]. Meanwhile, age was also identified as a risk factor for anthracycline-induced cardiotoxicity in CRC patients[17].

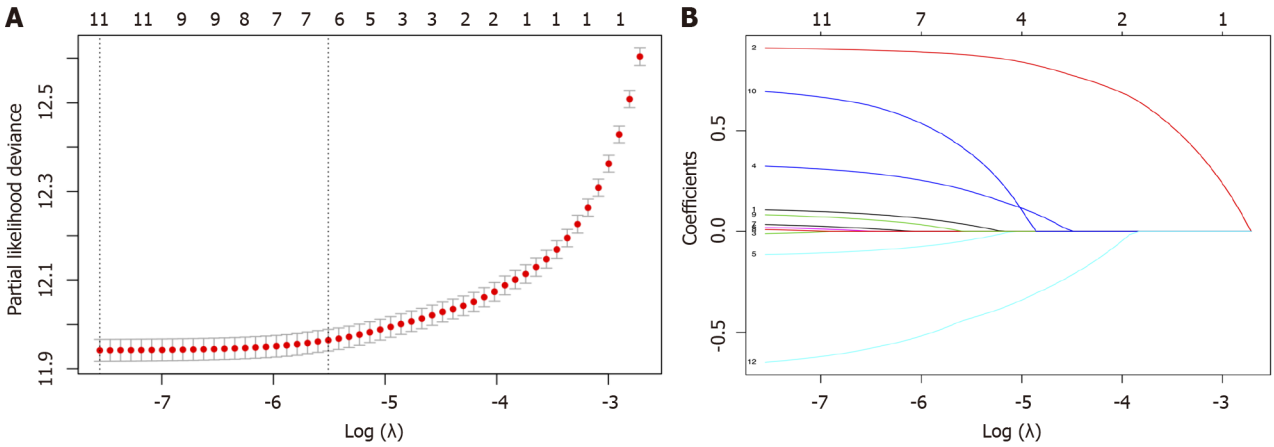

Figure 2 Lasso regression to determine the variables included in the model. A: Lasso regression search for the optimal coefficient; B: A 10x cross-validation approach used to determine lambda at the least partial likelihood deviance.

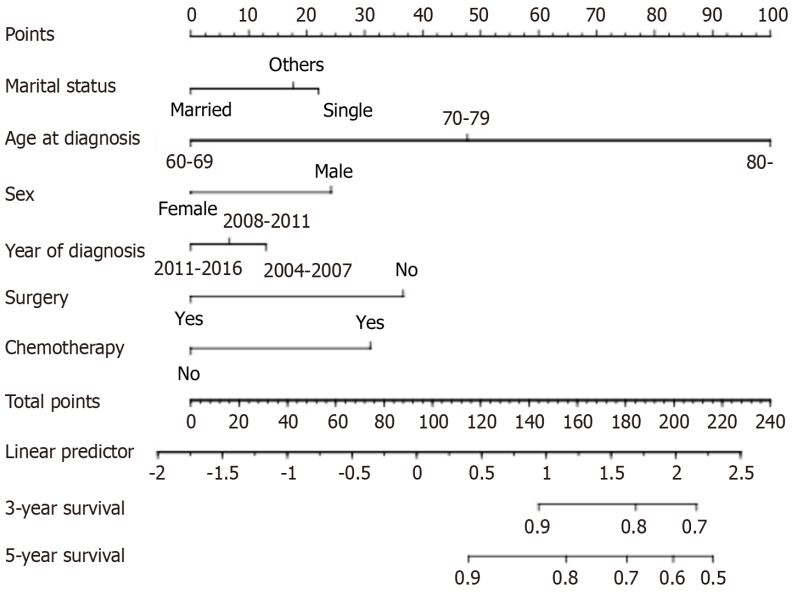

Figure 3 Nomogram to predict the 3- and 5-year cardiovascular disease survival of older patients of colorectal cancer.

Our results suggested that male patients had a positive correlation with the risk of CVD-specific mortality. Because estrogen lowers a woman's risk of CVD, they are typically protected by estrogen. Increased levels of oxidative stress may interfere with the mechanisms of DNA repair and was associated with higher rates of CRC and CVD[18]. Men are less resilient to oxidative stress than women and also have a higher risk of myocardial infarctions than women[19-21]. In addition, in our study, married status was also associated with reduced CVD-specific mortality in older patients with CRC. Married patients generally had better outcomes than single patients, which may be partly related to a favorable family environment[22].

An increasing number of older patients with CRC undergo surgery, chemotherapy, and/or radiotherapy. The improved anti-tumor systemic treatments resulted in longer survival time of patients with CRC[23]. However, the chemotherapeutic agents for CRC, such as oxaliplatin, 5-fluorouracil, cetuximab, and bavacizumab exhibit potential cardiotoxicity that may lead to a progressive increase in CVD deaths. Some studies have reported that a significant number of patients with CRC suffered CVD events following treatment with capecitabine, oxaliplatin, and bevacizumab [24-26]. Unfortunately, there are no specific chemotherapy regimens for patients with cancer in the SEER database, so we were unable to draw conclusions about the effects of specific chemotherapy regimens on CVD-specific mortality in this study. In the future, we aim to collect relevant data from other research centers for analysis to obtain more accurate results.

We developed a nomogram-based model for predicting the CVD-specific mortality in older patients with CRC based on six key prognostic variables, which is the first for CRC patients > 60 years old based on the SEER database. The model could be well applied in clinical work. This nomogram provides a visual and convenient assessment tool not only for the follow-up management of patients with cancer but also to ensure early intervention measures for such a high-risk population to improve the prognosis of patients and reduce the burden on healthcare resources. The nomogram-based

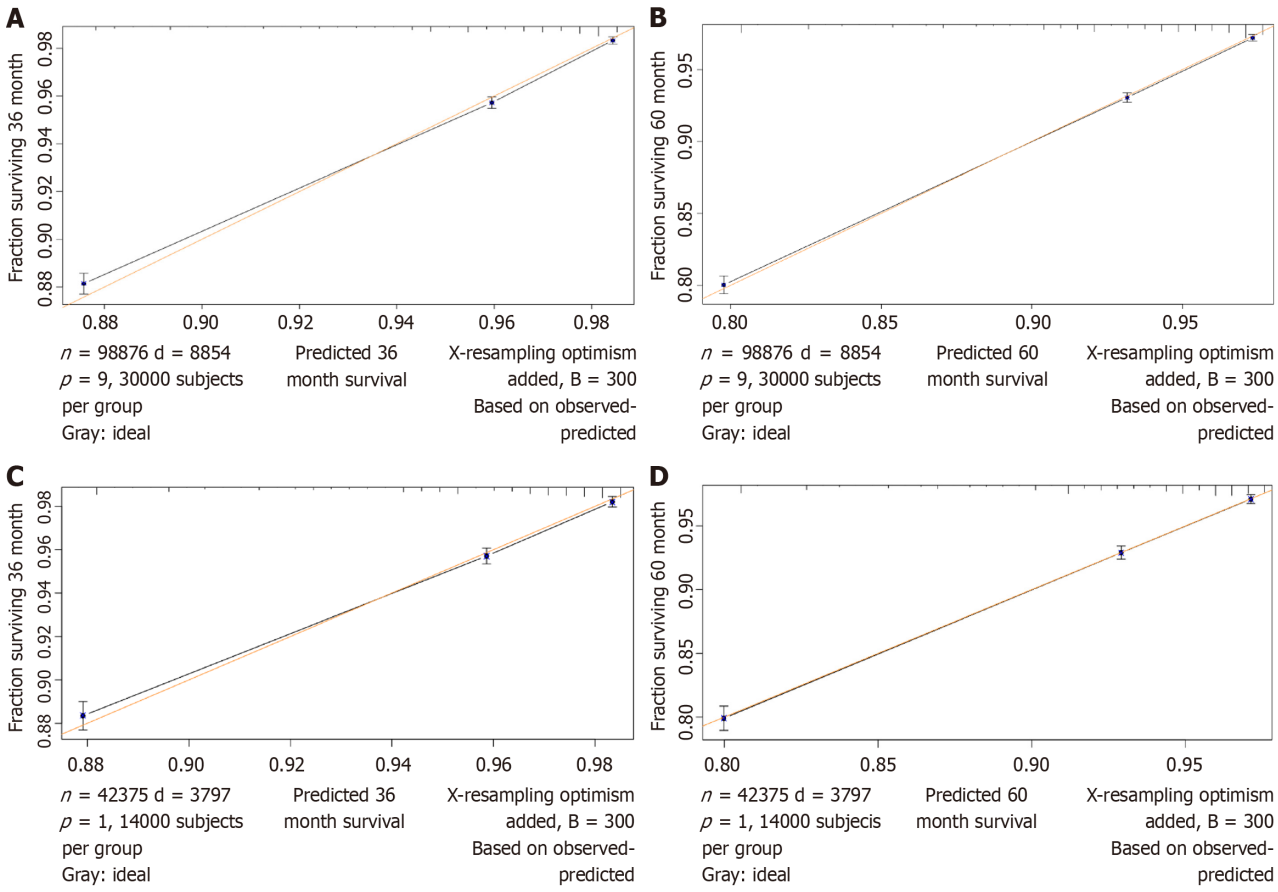

Figure 4 Calibration curves for the 3-year and 5-year cardiovascular disease survival. A and B: Training cohort; C and D: Testing cohort.

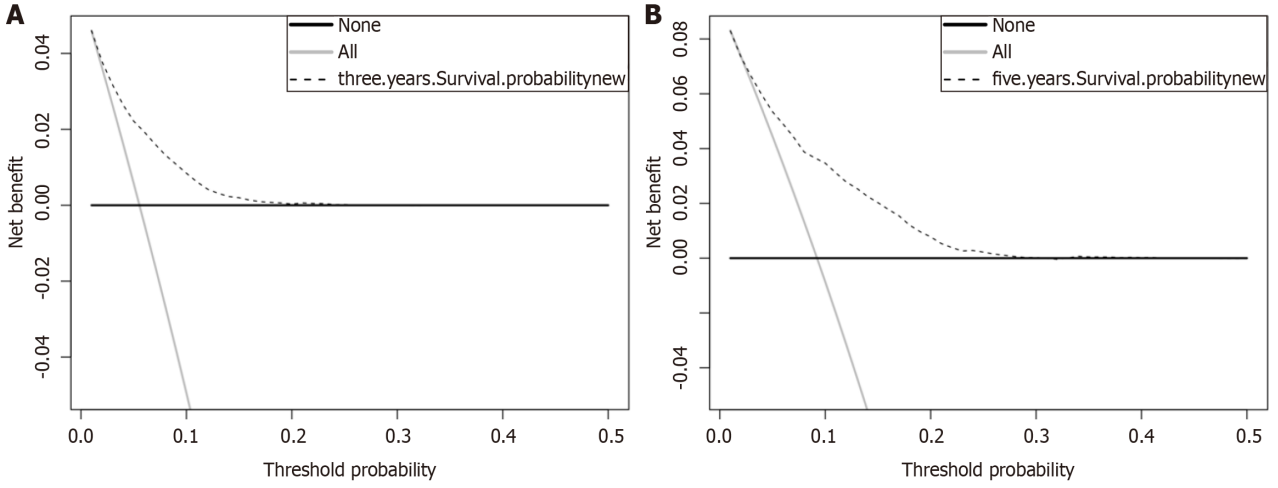

Figure 5 Decision curve analysis for the nomogram-based model. A and B: Predicting the prognosis of 3-year (A) and 5-year (B) cardiovascular disease survival in the testing cohort.

model emphasized the contributions of age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy. The nomogram-based model was verified by a training (C-index: 0.728) and testing (C-index: 0.734) cohort, indicating great diagnostic accuracy of the model. In addition, the DCA suggested that the estimated CVD-specific mortality threshold probability of a patient had a positive net benefit.

Older patients with CRC have a better cancer-specific prognosis, but the risk of CVD-specific death is still higher. Antitumor therapy could directly lead to CVD or increase the risk of CVD, which had a serious impact on the quality of life and health of patients with cancer. There is growing evidence showing the shared pathophysiology and overlapping risk factors between CRC and CVD in the field of cardio-oncology[27-29]. Cardio-oncology has explored an optimal approach to manage these patients *via* the active collaboration between oncologists and cardiologists[30]. Patients with CRC maybe benefit from clinical intervention, which could reduce the CVD events. In addition, this study also emphasizes the need

for continuous and active surveillance during patient survival. This finding supports the early intervention of cardiologists, and they are especially important in that future research will focus on early heart disease assessment and how active heart diseases care should be in older patients.

This study has some limitations. First, the SEER database lacked many important variables such as blood lipid data, height, weight, medical history, and chemotherapy regimens. Second, the SEER database includes data from many medical centers, and the data were hence heterogeneous. We have adopted strict inclusion and exclusion of indicators to reduce heterogeneity. Third, our nomogram currently lacks an external cohort for predictive efficacy. In the future, we aim to incorporate external cohorts to validate our nomogram.

CONCLUSION

The age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy were independent prognostic factors associated with CVD-specific mortality in older patients with CRC. The proposed nomogram-based model of the CVD-specific mortality could be used to predict the accurate prognosis for older patients with CRC and could be adopted to assist clinicians including oncologists and cardiologists to provide screening recommendations and choose an optimum treatment regimen.

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FOOTNOTES

Author contributions: Shen SH and Tan JY designed the research study; Shen SH and Tan JY performed the research. Shen SH and Tan JY analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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SYSTEMATIC REVIEWS

Tissue-source effect on mesenchymal stem cells as living biodrugs for heart failure: Systematic review and meta-analysis

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Abstract

BACKGROUND

Mesenchymal stem cells (MSCs), as living biodrugs, have entered advanced phases of clinical assessment for cardiac function restoration in patients with myocardial infarction and heart failure. While MSCs are available from diverse tissue sources, bone-marrow-derived MSCs (BM-MSCs) remain the most well-studied cell type, besides umbilical-cord-derived MSCs (UC-MSCs). The latter offers advantages, including noninvasive availability without ethical considerations.

AIM

To compare the safety and efficacy of BM-MSCs and UC-MSCs in terms of left ventricular ejection fraction (LVEF), 6-min walking distance (6MWD), and major adverse cardiac events (MACEs).

METHODS

Five databases were systematically searched to identify randomized controlled trials (RCTs). Thirteen RCTs (693 patients) were included using predefined eligibility criteria. Weighted mean differences and odds ratio (OR) for the changes in the estimated treatment effects.

RESULTS

UC-MSCs significantly improved LVEF *vs* controls by 5.08% [95% confidence interval (CI): 2.20%-7.95%] at 6 mo and 2.78% (95%CI: 0.86%-4.70%) at 12 mo. However, no significant effect was observed for BM-MSCs *vs* controls. No significant changes were observed in the 6MWD with either of the two cell types. Also, no differences were observed for MACEs, except rehospitalization rates, which were lower only with BM-MSCs (odds ratio 0.48, 95%CI: 0.24-0.97) *vs* controls.

CONCLUSION

UC-MSCs significantly improved LVEF compared with BM-MSCs. Their advant-

ageous characteristics position them as a promising alternative to MSC-based therapy.

Key Words: Cardiovascular disease; Heart disease; Mesenchymal stem cells; Umbilical cord stem cells

Core Tip: Mesenchymal stem cells (MSCs) are fast emerging as living biodrugs to repair and replace dysfunctional myocardium. While MSCs are available from diverse adult and fetal tissues, bone-marrow-derived MSCs (BM-MSCs; adult tissue source) and umbilical-cord-derived MSCs (UC-MSCs; fetal tissue source) remain the most well-studied types during recent clinical trials. The primary aim of this systematic review and meta-analysis was to evaluate the comparative safety and effectiveness of BM-MSC- and UC-MSC-based therapy in heart failure patients, analyzing left ventricular ejection fraction and 6-min walking distance as the primary functional and clinical outcomes.

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INTRODUCTION

Cardiovascular diseases (CVDs) remain the most common cause of morbidity and mortality worldwide despite recent advances in pharmacological disease management[1]. The akinetic fibrous scar that develops as part of the inefficient intrinsic repair mechanism in the heart after recurrent myocardial infarction (MI) is one of the critical factors responsible for putting the heart into the vicious cycle of remodeling, leading to heart failure (HF). Most contemporary therapeutic options, at best, can only provide symptomatic relief. In this regard, mesenchymal stem cell (MSC)-based therapy to repair and replace dysfunctional myocardium is fast emerging as a viable option and has progressed to advanced phases of clinical assessment[2].

MSCs were identified as a unique cell group characterized by preferential plastic surface adherence, specific surface marker expression, and trilineage differentiation potential[3]. They showed high proliferation and exceptional abilities to generate proangiogenic and anti-inflammatory paracrine factors[4]. Preclinical studies have demonstrated that MSCs possess a nonimmunogenic phenotype and the capacity to evade immunosurveillance[5]. These characteristics render them a choice for a cell-based therapy approach, and they are being reckoned as prototypes of the living biodrug family with some products already approved for different clinical conditions, such as Prochymal and Lomecel.

While MSCs are available from diverse adult and fetal tissues[6], bone-marrow-derived MSCs (BM-MSCs; adult tissue source) and umbilical-cord-derived (UC-MSCs; fetal tissue source) remain the most well-studied types during recent clinical trials. As of April 20, 2024, 59 clinical trials assessing MSCs for cardiac disease are registered on ClinicalTrials.gov, with 25 focusing explicitly on BM-MSCs. Nevertheless, most of these studies have reported less-than-expected results than the preclinical, experimental data[7]. The modest outcome may be attributed to various confounding factors, encompassing treatment-related factors, such as route of administration and cell dose [8,9], to the quality of cell preparation, such as donor age and health status[10,11]. However, UC-MSCs are readily accessible from medical waste for clinical applications without moral and ethical concerns[12]. Since the first reports of UC-MSCs, they have been extensively studied in experimental animal models of myocardial injury[13,14]. UC-MSCs have recently garnered more attention in clinical settings because of their advantages, including ready-to-use "off-the-shelf" availability, noninvasive collection, lack of ethical issues, younger age origin, and embryonic-cell-like characteristics[12,15,16]. Building upon near-ideal features and promising preclinical data, UC-MSCs have recently advanced to phase II pivotal trials for heart therapy.

We have conducted a rigorous systematic review comparing the clinical performance of BM-MSCs with UC-MSCs, which may be crucial to establishing a more reliable guide for designing future MSCs-based clinical trials. The primary aim of this systematic review and meta-analysis was to evaluate the comparative safety and effectiveness of BM-MSC- and UC-MSC-based therapy in HF patients by analyzing left ventricular ejection fraction (LVEF), 6-min walking distance (6MWD) as the primary functional and clinical outcomes. We examined the safety profile of the two cell types using the major adverse cardiovascular events (MACEs), *i.e.*, cardiac death, rehospitalization for HF, recurrent MI, infract-vessel revascularization procedure, arrhythmias, and stroke as the secondary outcomes.

MATERIALS AND METHODS

Protocol registration and search strategies

A search strategy was conducted to identify relevant trials based on the Preferred Reporting Item for Systematic Reviews

and Meta-Analysis guidelines[17]. The protocol was registered at the International Prospective Register of Systematics Reviews (PROSPERO; CRD4202348206). Our search strategy encompassed PubMed, Cochrane database, ClinicalTrials.gov, Embase, and ScienceDirect databases from their inception to April 2024. The search terms included common text words and Medical Subject Headings, such as myocardial infarction, coronary artery disease, heart failure, ischemic cardiomyopathy, non-ischemic cardiomyopathy, dilated cardiomyopathy, decompensated heart failure, mesenchymal stem cells, umbilical cord mesenchymal stromal cells, and bone marrow mesenchymal stem cells. These terms were also combined using specific algorithms, such as umbilical cord mesenchymal stem cells and heart failure. Manual searches were conducted to explore potential trials among the selected articles. No language restrictions were applied to the investigation.

Eligibility criteria

To be eligible for inclusion, a study met the following criteria: (1) It should be a phase I/II randomized controlled clinical trial that investigates the efficacy and safety of UC-MSCs and BM-MSCs; (2) The study involved patients diagnosed with MI, HF, or cardiomyopathy; (3) The intervention group should be treated with UC-MSCs or BM-MSCs; (4) There should be a control group; (5) The study should report at least one of the following clinical outcomes: LVEF, 6MWD test, death, readmission for HF, and MACEs (arrhythmia, recurrent MI, and stroke); and (6) The follow-up duration should be > 6 mo. Only studies that met the inclusion criteria and were complete or had available full text were included. All other randomized controlled trials (RCTs) were excluded from the study.

Data extraction

Three coauthors independently assessed the eligibility of the studies for meta-analysis using the inclusion/exclusion criteria and a predefined data-extraction sheet. Each included study was examined, and the following variables were extracted: (1) First author; (2) year of publication; (3) trial location (country); (4) intervention type (BM-MSCs or UC-MSCs); (5) source of stem cells (autologous *vs* allogenic); (6) sample size; (7) sex; (8) mean sample age; (9) comorbidities; (10) follow-up period for key endpoint measurements; (11) dose (number of cells transferred in millions); (12) cell delivery mode (*e.g.*, intravenous, intramyocardial, or intracoronary infusion); (13) cell status (fresh or frozen); (14) New York Heart Association classification of study participants at baseline; (15) study end-point assessment method/tools (*e.g.*, electrocardiogram, echocardiogram, magnetic resonance imaging, cardiac computed tomography, and single-photon emission computed tomography); (16) LVEF (mean ± SD); (17) 6MWD (mean ± SD); and (18) MACEs.

Quality assessment

The methodological quality of the included RCTs was evaluated using the Cochrane Collaboration tool, which assessed the risk of bias based on the following criteria: sequence generation randomness, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective reporting, and other potential sources of bias. Each study was categorized as having low risk, high risk, or unclear risk of bias for each criterion. The overall risk of bias was determined by considering all the criteria and presenting it as a risk of bias graph.

Statistical analysis

Two intervention groups from one of the UC-MSC trials were combined into one group[18]. One group received human UC-MSCs (hUC-MSCs) encapsulated in a collagen hydrogel, while the other received only hUC-MSCs. We calculated and presented fixed-effects Peto odds ratios (OR) with 95% confidence interval (CI) for dichotomous data of adverse events, including death, MACEs, and rehospitalization. We chose the Peto OR method due to the anticipated rarity of adverse events reported across the included studies[19]. This method adds a continuity correction factor of 0.5 for any cells containing zero events, allowing for better estimating rare events. We calculated random-effect mean difference pooled effects for continuous data, presented with 95%CI. This included the change in LVEF and 6MWD from baseline to 6 and 12 mo of follow-up. We used a random-effect model due to expected differences in the study samples and countries. We conducted a weighted mean difference (WMD) meta-analysis as LVEF and 6MWD were reported in the same units across the studies (*i.e.*, percentages and meters).

For continuous outcomes, the data reported in CIs or SE were converted to SD using the Cochrane Handbook equations[20]. When examining the mean ± SD difference from baseline to 6 and 12 mo of follow-up, we found that only one of the UC-MSCs studies[21] provided the mean ± SD change from baseline values. To ascribe the missing change in SD for LVEF, we applied a correlation coefficient of 0.65 derived from the study by Gao *et al*[21] as recommended by the Cochrane Handbook[20,21]. None of the UC-MSCs studies reported the change in mean ± SD for 6MWD; hence, we used a conservative value of 0 as the correlation coefficient to calculate the change in SD[22]. For the BM-MSCs studies that did not report the change in mean ± SD, we used a correlation coefficient value of 0.75 derived from Bolli *et al*[23] for both LVEF and 6MWD changes in SD calculations.

Subgroup analysis was conducted on studies involving BM-MSCs to explore the impact of patients' conditions on the significance of the pooled effects of our primary outcome, LVEF. The analysis focused on two subgroups: HF and MI. However, the same subgrouping could not be performed on the UC-MSCs studies due to the limited number of studies available. Only one study focused on MI patients, while the remaining focused on HF patients.

A new methodological approach was implemented to compare MSCs from the two tissue sources and mitigate any potential overestimation of the effect of the control arm in some studies compared to others. The data from the control arm across all included RCTs were consolidated to derive a unified mean (± SD). Using a similar strategy, the intervention arms (UC-MSCs and BM-MSCs) were analyzed, combining the means (± SDs) reported in the relevant RCTs for each cell type into a single combined mean (± SD). Subsequently, the combined mean (± SD) for each cell type was

compared with the unified control, providing insights into the performance of both cell types in the unified control group. This methodology facilitated a comprehensive evaluation of the effectiveness of UC-MSCs and BM-MSCs compared to the same established control. All calculations used were according to the formulas provided by the Cochrane Handbook[20].

The risk of publication bias was assessed by creating funnel plots of our primary functional outcome, LVEF, in UC-MSCs and BM-MSCs studies. We then evaluated asymmetry, indicating the publication bias.

Statistical heterogeneity was assessed using the I^2 statistic. I^2 < 25% was considered unimportant. A 25%-75% value indicated moderate heterogeneity, and 75%-100% considerable heterogeneity[20]. All statistical data analysis was performed using RevMan 5.4.1 software[24]. $P \leq 0.05$ was considered statistically significant.

RESULTS

Eligible studies

Figure 1 summarizes the process of including studies for the meta-analysis. The literature search across multiple databases yielded 807 potentially relevant studies. Title and abstract screening retained 106 studies, of which 93 were excluded for reasons given in Figure 1, leaving 13 eligible RCTs for analysis.

The risk of bias included in the studies was assessed using the Cochrane Collaboration risk-of-bias tool. The studies were evaluated for selection, performance, detection, attrition, and reporting biases. A risk of bias graph was generated to present the review authors' judgments for each domain in the included studies (Figure 2).

Characteristics of RCTs included in the meta-analysis

Details of the characteristics of included trials are presented in Tables 1, 2 and 3 for UC-MSCs-based and BM-MSCs-based trials, respectively. The 13 RCTs used for meta-analysis spanned from 2009 to 2020, including four RCTs evaluating UC-MSCs, eight RCTs assessing BM-MSCs, and one RCT utilizing both cell types[25]. Locations of the RCTs were Türkiye [25], China[18,22,26,27], Chile[28], India[29], USA[24,30], Denmark[31], Netherlands[32], and South Korea[33].

In the five UC-MSC RCTs (296 patients), 160 patients were in the intervention group, while 130 were in the control group. Male percentages ranged from 78%-100% (intervention group) to 58%-100% (control group). Similarly, in the eight BM-MSC-based RCTs (397 patients), 197 patients were in the intervention group, and 200 patients were in the control group. Males comprised 43%-100% (intervention) and 24%-100% (control). The follow-up duration in the RCTs ranged from 1 to 18 mo (Tables 1, 2 and 3).

Regarding cell characteristics, six RCTs used frozen MSCs, and seven used fresh MSCs. BM-MSCs were obtained from allogeneic[24,29,30], or autologous[25,27,31-33] tissue sources. Diverse routes of administration were used, including intravenous[29,30], intramyocardial[24,25,31,32], intracoronary[27,33] (Tables 4 and 5).

The functional outcome: LVEF

Four of five UC-MSCs studies (intervention group = 102; control group = 72) and six of nine BM-MSCs studies (intervention group = 115; control group = 115) reported the change of LVEF after 6 mo of follow-up and were included in the meta-analysis. The pooled effect of UC-MSCs on LVEF during 6 mo follow-up showed a significant improvement of 5.08% compared to its control group, with moderate heterogeneity (MD 5.08, 95%CI: 2.20%-7.95%; $P = 0.0005$; $I^2 = 61\%$) (Figure 3A). The pooled effect of BM-MSCs changed LVEF insignificantly compared to its control group (MD 2.70%, 95%CI: -1.40 to 2.83; $P = 0.11$; $I^2 = 81\%$). Although both subgroups of BM-MSCs according to the patient's condition did not reach the significance level, BM-MSC-based intervention in HF patients showed a higher improvement (MD 4.53%, 95%CI: -0.85 to 9.91; $P = 0.10$; $I^2 = 85\%$) compared to the MI patients (MD 0.72%, 95%CI: -1.40 to 2.83; $P = 0.51$; $I^2 = 0\%$) (Figure 3B). When the combined mean (± SD) of each cell type was compared with the unified control group, both cell types showed a statistically significant improvement in LVEF with UC-MSCs achieving 5.53% improvement (MD 5.53%, 95%CI: 3.45-7.61, $P < 0.0001$) and 1.54% LVEF improvement with BM-MSCs (MD 1.54%, 95%CI: 0.06-.02, $P = 0.04$) (Supplementary Figure 1).

Four of five UC-MSCs studies with a total of 130 patients in the intervention group and 101 in the control group were followed up for 12 mo[18,22,25,28]. The pooled effect of their mean LVEF showed a significant improvement of 2.78% of LVEF in the intervention group compared to its control group (MD 2.78, 95%CI: 0.86-4.70; $P = 0.004$; $I^2 = 16\%$) (Figure 4A). On the contrary, after 12 mo of follow-up, the five BM-MSC studies showed that 63 patients in the BM-MSC intervention group experienced a 4.35% improvement in LVEF within the HF subgroup. This improvement was significantly greater compared to the control group (99 patients) with moderate heterogeneity (MD 4.34, 95%CI: 0.66-8.03; $P = 0.02$; $I^2 = 44\%$). In contrast to the HF group, no significant LVEF change was observed with BM-MSCs in the MI subgroup (MD -0.16, 95%CI: -5.85 to 5.52; $P = 0.96$; $I^2 = 87\%$) (Figure 4B).

When the combined means and SDs of each cell type were compared with the unified control, UC-MSCs improved LVEF by 1.18% (MD 1.18%, 95%CI: -0.43 to 2.79, $P = 0.15$), but without reaching the level of statistical significance. Combined means and SDs of BM-MSCs showed a significant improvement in LVEF by 2.38% compared to the unified control group (MD 2.38%, 95%CI: 0.38-4.38 $P = 0.02$) (Supplementary Figure 2). A funnel plot of LVEF was plotted to assess publication bias. The distribution of the studies showed asymmetry, suggesting a potential publication bias (Supplementary Figure 3).

Table 1 Baseline characteristics of randomized clinical trials included in the meta-analysis for mortality in umbilical-cord-derived mesenchymal-stem-cell-based heart therapy, *n* (%)

		Gao *et al*[21], 2015 (China)	He *et al*[18], 2020 (China)	Zhao *et al*[26], 2015 (China)	Bartolucci *et al*[28], 2017 (Chile)	Ulus *et al*[25], 2020 (Türkiye)
Study type		RCT	RCT	RCT	RCT	Open-label RCT
Phase		I/II	I	I/II	I/II	I/II
Sample size	Total	116	50	59	30	41
	Intervention (male)	58 (94.8)	32 (78.12)	30 (80.0)	15 (80.0)	25 (100)
	Control (male)	58 (87.9)	12 (58.30)	29 (65.5)	15 (93.3)	16 (100)
Mean age (mean ± SD)	Intervention	57.3 ± 9.90	59.6 (7.9)/63.6 (8.6)	52.90 ± 16.32	57.33 ± 10.05	61.8 ± 10
	Control	56.7 ± 12.95	65.2 (7.9)	53.21 ± 11.46	57.20 ± 11.64	65.3 ± 6.8
Mean BMI (mean ± SD)	Intervention	24.9 ± 2.28	25.5 ± 3.3 /24.4 ± 3.3	N/A	29.12 ± 2.88	26.5 ± 4.5
	Control	25.4 ± 2.28	23.59 ± 2.28	N/A	29.52 ± 4.00	26.6 ± 4.8
Number of smokers	Intervention	34 (58.6)	4 (25.0)/7 (43.8)	N/A	7 (46.7)	21 (84)
	Control	32 (55.2)	3 (25.0)	N/A	4 (26.7)	15 (88.2)
HTN	Intervention	33 (56.9)	10 (62.5)/14 (87.5)	N/A	7 (46.7)	15 (60)
	Control	26 (44.8)	9 (75.0)	N/A	8 (53.3)	11 (64.7)
DM	Intervention	17 (29.3)	8 (50.0)/4 (25.0)	N/A	5 (33.3)	16 (66.7)
	Control	14 (24.1)	8 (66.7)	N/A	7 (46.7)	9 (52.9)
NYHA; I (*n*), II (*n*), III (*n*), IV (*n*)	Intervention	N/A	III (4 / 8), IV (12 / 8)	N/A	2.03 ± 0.61	1.9 ± 0.44
	Control	N/A	III (7) IV (5)	N/A	1.67 ± 0.49	2.1 ± 0.37
Comparison		Placebo	CABG only	HF drugs only	Placebo	CABG only
Follow-up, months		1, 4, 12 and 18 mo	3, 6 and 12 mo	1 and 6 mo	3, 3, 6 and 12 mo	1, 3, 6 and 12 mo
Assessment modality (yes/no)	ECG	Yes	-	Yes	Yes	Yes
	Echo	Yes	-	Yes	Yes	Yes
	MRI	No	Yes - CMR	-	Yes - CMR	Yes
	Cardiac CT	Yes	-	-	-	No
	SPECT	Yes	-	-	-	Yes
Measured outcomes		Safety and adverse event (primary), efficacy, and LV functions LVEF (secondary)	Serious adverse events at 12 mo (primary), the efficacy of hUC-MSCs and collagen scaffold assessed according to the CV-CMR-based LVEF and infarct size at 3, 6 and 12 mo after treatment, and NYHA (secondary)	Changes in LVEDD, LVEF, BNP, 6MWD, symptoms of HF, death, and adverse events	Safety: Adverse events after IV infusion -/-. Efficacy: (primary). Change in LVEF in ECHO, changes in -(LVESV) & (LVEDV) at ECHO; LVEF, LVESV, and LVEDV in CMR; NYHA score (secondary)	LVEF, LV remodeling, myocardial mass, 6MWD, NYHA score change

HUC-MSCs: Human umbilical cord mesenchymal stem cells; HT: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; CABG: Coronary artery bypass grafting; HF: Heart failure; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; MI: Myocardial infarction; 6MWD: 6-min walking distance test; N/A: Not available; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; BNP: Brain natriuretic peptide; ECG: Electrocardiogram; Echo: Echocardiogram; MRI: Magnetic resonance imaging; CT: Computed tomography; SPECT: Single-photon emission computed tomography.

Clinical outcome: 6MWD

Two of five studies on UC-MSCs, with 55 patients in the intervention group and 45 patients in the control group, were followed up[25,26]. Similarly, three of nine BM-MSCs studies with 60 patients in the intervention group and 49 patients in the control group = 49) reported 6MWD data[24,25,30]. The pooled analysis found no significant difference in 6MWD between the intervention and its respective control groups for either UC-MSCs or BM-MSCs. For BM-MSCs, the mean difference was -6.08 m (95%CI: -46.56 to 34.38; P = 0.77; I^2 = 51%) (Supplementary Figure 4A). Similarly, for UC-MSCs, the mean difference was 53.25 m (95%CI: -81.61 to 188.11, P = 0.44, I^2 = 83%) (Supplementary Figure 4B). Both results indicate

Table 2 Baseline characteristics of randomized clinical trials included in the meta-analysis of bone-marrow-derived mesenchymal-stem-cell-based cardiac therapy, *n* (%)

		Chullikana *et al*[29], 2015 (India)	Hare *et al*[30], 2009 (USA)	Heldman *et al*[34], 2014 (USA)	Mathiasen *et al*[31], 2015 (Denmark)	Xiao *et al*[27], 2017 (China)
Study type		RCT	RCT	Open label RCT	RCT	Open label RCT
Phase		I/II	I	I/II	I/II	I/II
Condition		MI	MI	HF	HF	HF
Sample size	Total	20	53	30	60	37
	Intervention (male)	10 (100)	34 (82.4)	19 (94.7)	40 (90)	17 (70)
	Control (male)	10 (80)	19 (78.9)	11 (90.9)	20 (70)	20 (70)
Mean age (mean ± SD)	Intervention	47.31 ± 12.10	59 ± 12.3	57.1 ± 10.6	66.1 ± 7.7	51.6 ± 12.2
	Control	47.79 ± 6.48	55 ± 10.2	60.0 ± 12.0	64.2 ± 10.6	54.4 ± 11.6
Mean BMI (mean ± SD)	Intervention	23.32 ± 3.74	29.8 ± 6.7	N/A	29.8 + 4.7	N/A
	Control	24.86 ± 1.88	30.3 ± 4.3	N/A	28.7 ± 5.3	N/A
Number of smokers	Intervention	N/A	3 (8.8)	14 (73)	7 (17)	N/A
	Control	N/A	2 (10.5)	9 (81.9)	1 (5)	N/A
HTN	Intervention	N/A	16 (17.6)	12 (63.2)	0	4 (23)
	Control	N/A	9 (47.4)	6 (54.5)	0	7 (35)
DM	Intervention	N/A	6 (17.6)	3 (15.8)	15 (37)	5 (29.4)
	Control	N/A	1 (5.3)	3 (27.3)	3 (15)	6 (30)
NYHA; I (*n*), II (*n*), III (*n*), IV (*n*)	Intervention	N/A	N/A	I (5)/II (12)/III (2)	II (11)/III (29)	II
	Control	N/A	N/A	I (2)/II (5)/III (3)	II (5)/III (15)	II
Comparison		Placebo (multiple electrolytes injection)	Placebo	HF treatments	HF treatments	HF treatments
Follow-up		6 mo to 2 yr	6 mo	12 mo	6 mo	12 mo
Assessment modality (yes/no)	ECG	No	Yes	Yes	No	Yes
	Echo	Yes	Yes	No	No	Yes
	MRI	Yes	Yes	Yes	Yes	No
	Cardiac CT	No	Yes	Yes	Yes	No
	SPECT	Yes	No	No	No	Yes
Measured outcomes		Adverse events, LVEF (Echo and SPECT), total perfusion score, and total infarct volume	Safety, adverse events, LVEF (Echo), and 6MWD	Adverse events (primary), 6MWD, NYHA, and LV parameters (secondary)	LVESV (primary), LVEF, NYHA, 6MWD, and LV parameters (secondary)	LVEF, NYHA, LVEDV, and MAE are primary endpoints

HUC-MSCs: Human umbilical cord mesenchymal stem cells; HT: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; CABG: Coronary artery bypass grafting; HF: Heart failure; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; MI: Myocardial infarction; 6MWD: 6-min walking distance test; N/A: Not available; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; BNP: Brain natriuretic peptide; ECG: Electrocardiogram; Echo: Echocardiogram; MRI: Magnetic resonance imaging; CT: Computed tomography; SPECT: Single-photon emission computed tomography.

no significant treatment effect of either stem cell type on 6MWD compared to their control group.

When compared with the unified control group, UC-MSCs showed a non significant improvement of 7.47 m (MD 7.47, 95%CI: -20.69 to 35.63, P = 0.60). However, the comparison between the combined means and SDs of BM-MSCs and the unified control group resulted in a significant improvement of 49.74 m in the BM-MSCs group (MD 49.74, 95%CI: 5.53-93.95, P = 0.03) (Supplementary Figure 4C).

Table 3 Baseline characteristics of randomized clinical trials included in the meta-analysis of bone-marrow-derived mesenchymal-stem-cell-based cardiac therapy, *n* (%)

		Ulus *et al*[25], 2020 (Türkiye)	Rodrigo *et al*[32], 2013 (Netherlands)	Kim *et al*[16], 2018 (South Korea)	Bolli *et al*[23], 2020 (USA)
Study type		Open-label RCT	RCT	RCT	RCT
Phase		I/II	I/II	I	I
Condition		CIC	MI	MI	HF
Sample size	Total	28	54	26	31
	Intervention (male)	12 (100)	9 (78)	14 (100)	14 (43)
	Control (male)	16 (100)	45 (78)	12 (100)	17 (24)
Mean age (mean ± SD)	Intervention	56.9 ± 5.20	56 ± 8	55.3 ± 8.6	54.7 ± 12.8
	Control	65.3 ± 6.8	61 ± 11	57.8 ± 8.9	58.2 ± 11.2
Mean BMI (mean ± SD)	Intervention	26.2 ± 3.12	N/A	N/A	30.2 ± 9.0
	Control	26.6 ± 4.8	N/A	N/A	30.4 ± 6.5
Number of smokers	Intervention	11 (91.6)	6 (67)	5 (35.7)	5 (36)
	Control	15 (88.2)	19 (42)	5 (41.7)	3 (18)
HTN	Intervention	6 (50)	4 (44)	5 (35.7)	6 (43)
	Control	11 (64.7)	18 (40)	5 (41.7)	10 (59)
DM	Intervention	4 (33.3)	1 (11)	3 (21.4)	3 (21)
	Control	9 (52.9)	5 (11)	2 (16.7)	5 (29)
NYHA; I (*n*), II (*n*), III (*n*), IV (*n*)	Intervention	2.2 ± 0.6	N/A	N/A	II (13), III (1)
	Control	2.1 ± 0.37	N/A	N/A	II (13), III (4)
Comparison		CABG only	No placebo (optimal MI treatment)	No placebo (optimal MI treatment)	HF treatments
Follow-up duration		1, 3, 6, and 12 mo	3, 6, 12 mo, 4, 5 years	4 and 12 mo	6 and 12 mo
Assessment modality (Yes/no)	ECG	Yes	Yes - Holter	No	Yes
	Echo	Yes	Yes	Yes	No
	MRI	Yes	No	No	Yes - CMR
	Cardiac CT	No	No	No	No
	SPECT	Yes	Yes	Yes	No
Measured outcomes		LVEF, LV remodeling, myocardial mass, 6MWD, NYHA score	Safety and feasibility of IM delivery after PCI for MI (primary). Efficacy regarding change in infarct size, LVEF, LVEDV, and LVESV (secondary)	Absolute changes in global LVEF from baseline to 4 months after PCI using SPECT, Echo changes in global LVEF at 12 mo (primary). Changes in LVEDV, LVESV, and MACE (secondary)	Safety and feasibility of allogenic MSC in population (primary). Effects of allogenic MSC on LV function (LVEF, LVEDV, LVESV, scar), morphology, and functional status (6MWD, MLHFQ) (secondary)

MSCs: Mesenchymal stem cells; HT: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; MAE: Major adverse events; MACE: Major adverse cardiac events; CABG: Coronary artery bypass grafting; HF: Heart failure; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; MI: Myocardial infarction; 6MWD: 6-min walking distance test; N/A: Not available; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; ECG: Electrocardiogram; Echo: Echocardiogram; MRI: Magnetic resonance ımaging; CT: Computed tomography; SPECT: Single-photon emission computed tomography; MLHFQ: Minnesota living wıth heart failure questionnaire.

Table 4 Intervention characteristics of randomized controlled trials of umbilical-cord-derived mesenchymal stem cells

Refs	Cell type	Cell condition	MSCs dose and volume	Route of delivery	Concurrent procedure (if any)
He *et al*[18]	WJUC-MSCs	Frozen	1×10^8/1.5-2.5 mL +/- 1 mL collagen scaffold	IM	CABG for all groups
Zhao *et al*[26]	UC-MSCs	N/S	N/S	IC	N/A
Bartolucci *et al*[28]	WJUC-MSCs	Frozen	1×10^6/kg in 100 mL	IV	N/A
Ulus *et al*[25]	UC-MSCs	Frozen	23×10^6	IM	CABG for all groups
Gao *et al*[21]	WJUC- MSCs	Fresh	6×10^6	IC	N/A

CABG: Coronary artery bypass grafting; N/A: Not available; N/S: Not specified; IC: Intracoronary; IM: Intramyocardial; IV: Intravenous; PCI: Percutaneous coronary intervention; WJUC-MSCs: Wharton's Jelly umbilical cord mesenchymal stem cells; UC-MSCs: Umbilical cord-derived mesenchymal stem cells; MSCs: Mesenchymal stem cells.

Table 5 Intervention characteristics of randomized controlled trials of bone-marrow-derived mesenchymal stem cells

Refs	Cell type	Cell condition	Cell source	MSCs dose and volume	Route of delivery	Concurrent procedure (if any)
Chullikana *et al*[29]	BM-MSCs	Frozen	Allogenic	2 million cells/kg, 0.5 mL/kg	IV	N/A
Hare *et al*[30]	BM-MSCs	Frozen	Allogenic	0.5, 1.6, and 5.0×10^6	IV	N/A
Heldman *et al* [34]	BM-MSCs	Fresh	Autologous	N/A	IC	PCI
Mathiasen *et al*[31]	BM-MSCs	Fresh	Autologous	$77.5 \pm 67.9 \times 10^6$ in 10-15 injections	IM	N/A
Xiao *et al*[27]	BM-MSCs	Fresh	Autologous	4.9×10^8	IC	N/A
Ulus *et al*[25]	BM-MSCs	Fresh	Autologous	70×10^7	IM	CABG
Rodrigo *et al*[32]	BM-MSCs	Fresh	Autologous	$31 \pm 2 \times 10^6$ IN 10-12 injections	IM	N/A
Kim *et al*[16]	BM-MSCs	Fresh	Autologous	$7.2 \pm 0.90 \times 10^7$	IC	N/A
Bolli *et al*[23]	BM-MSCs	Frozen	Allogenic	1×10^8 *via* 20 TC injections	IM	N/A

BM-MSCs: Bone marrow mesenchymal stem cells; CABG: Coronary Artery Bypass Grafting; N/A: Not available; IC: Intracoronary; IM: Intramyocardial; IV: Intravenous; PCI: Percutaneous Coronary Intervention; MSCs: Mesenchymal stem cells.

Safety outcome: MACEs

Mortality: Four of five UC-MSCs studies (n = 246)[22,25,26,28] and six of nine BM-MSCs studies (n = 206)[24,25,27,29,31,34] reported on mortality during the follow-up period. No significant difference in the OR of mortality between the intervention and respective control group of UC-MSCs studies (Peto OR 0.35, 95%CI: 0.27-1.03; P = 0.06; I^2 = 0%) (Figure 5A) and BM-MSCs studies (Peto OR 0.74; 95%CI: 0.22-2.54; P = 0.64; I^2 = 0%) (Figure 5B). Similarly, both cell types did not significantly improve the mortality rate compared to the unified control.

MACEs: Four of five UC-MSCs studies (n = 246)[22,25,26,28] and eight of nine BM-MSCs studies (n = 285)[24,25,27,29-31,33,34] reported the incidence of MACEs, including angina, supraventricular tachycardia, ventricular tachycardia, and revascularization of MI. No significant effect was observed in the pooled OR of UC-MSCs studies (Peto OR 1.39; 95%CI: 0.42-4.60; P = 0.59; I^2 = 0%) (Figure 5C) and BM-MSCs studies (Peto OR 0.53; 95%CI: 0.27-1.03; P = 0.06; I^2 = 0%) between the intervention and control groups (Figure 5D).

When both cell types are compared with the unified control arm, the UC-MSCs studies demonstrated a significant reduction in the incidence of MACEs by an OR of 0.27 (0.27, 95%CI: 0.13-0.55, P = 0.0003). In contrast, the BM-MSCs studies did not significantly affect the MACE OR (1.41, 95%CI: 0.90-2.20, P = 0.13) (Supplementary Figure 5A).

Rehospitalization

Four of five UC-MSCs studies (n = 247)[18,22,26,28], and four of nine BM-MSCs studies (n = 182)[24,30,31,34], reported data on rehospitalization of the enrolled patients. UC-MSCs studies reported a nonsignificant difference between the intervention and control groups with a Peto OR of 0.62 (95%CI: 0.24-1.60; P = 0.31; I^2 = 17%) (Figure 5E). Analysis of BM-

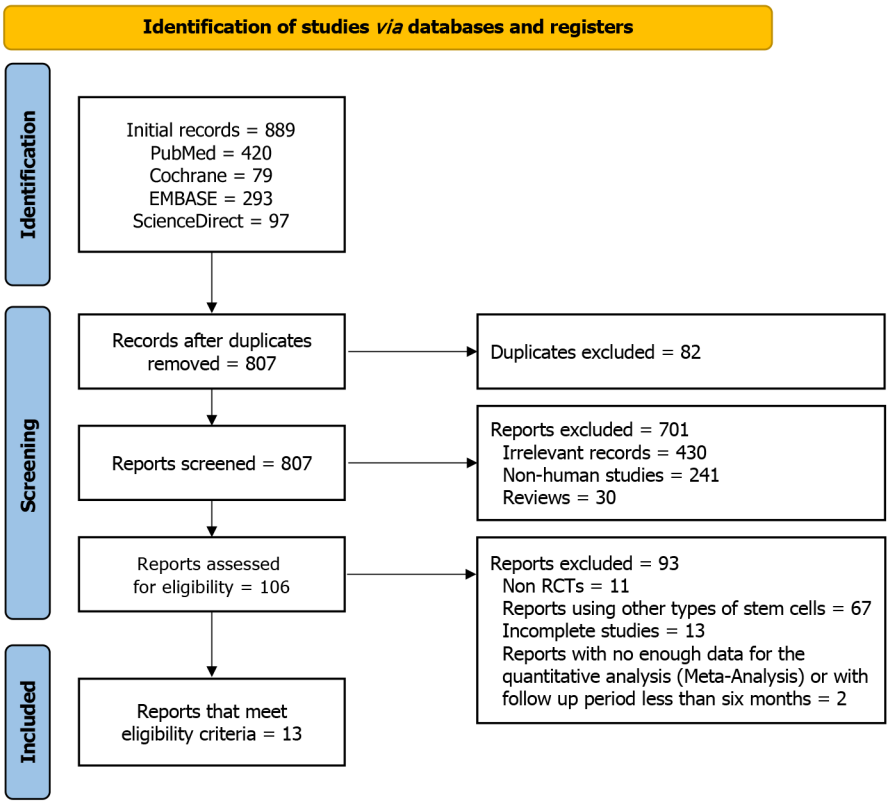


Figure 1 Study selection flow diagram of preferred reporting item for systematic reviews and meta-analysis. RCTs: Randomized controlled trials.

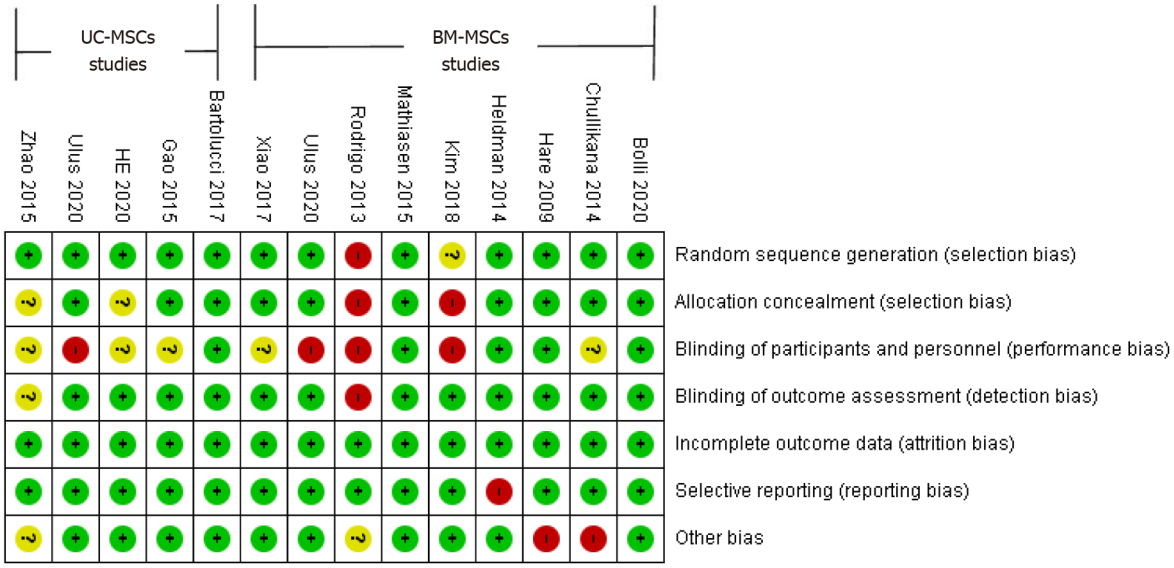


Figure 2 Risk of bias assessment graph. UC-MSCs: Umbilical-cord-derived mesenchymal stem cells; BM-MSCs: Bone-marrow-derived mesenchymal stem cell.

MSCs studies showed a significant reduction of rehospitalization rates by 52% and Peto OR of 0.48 (95%CI: 0.24-0.97; P = 0.04; I^2 = 39%) (Figure 5F). These findings suggest that BM-MSCs demonstrated a protective effect in the intervention group, resulting in a lower rehospitalization rate than their respective control group.

Compared to the unified control group, the UC-MSCs studies showed a significant reduction in the rehospitalization rate with an OR of 0.31 (95%CI: 0.14-0.66, P = 0.003). However, the BM-MSCs significant reduction in rehospitalization rate compared to its respective control was not maintained with the unified control (Peto OR 1.30, 95%CI: 0.73-2.31, P = 0.38) (Supplementary Figure 5B).

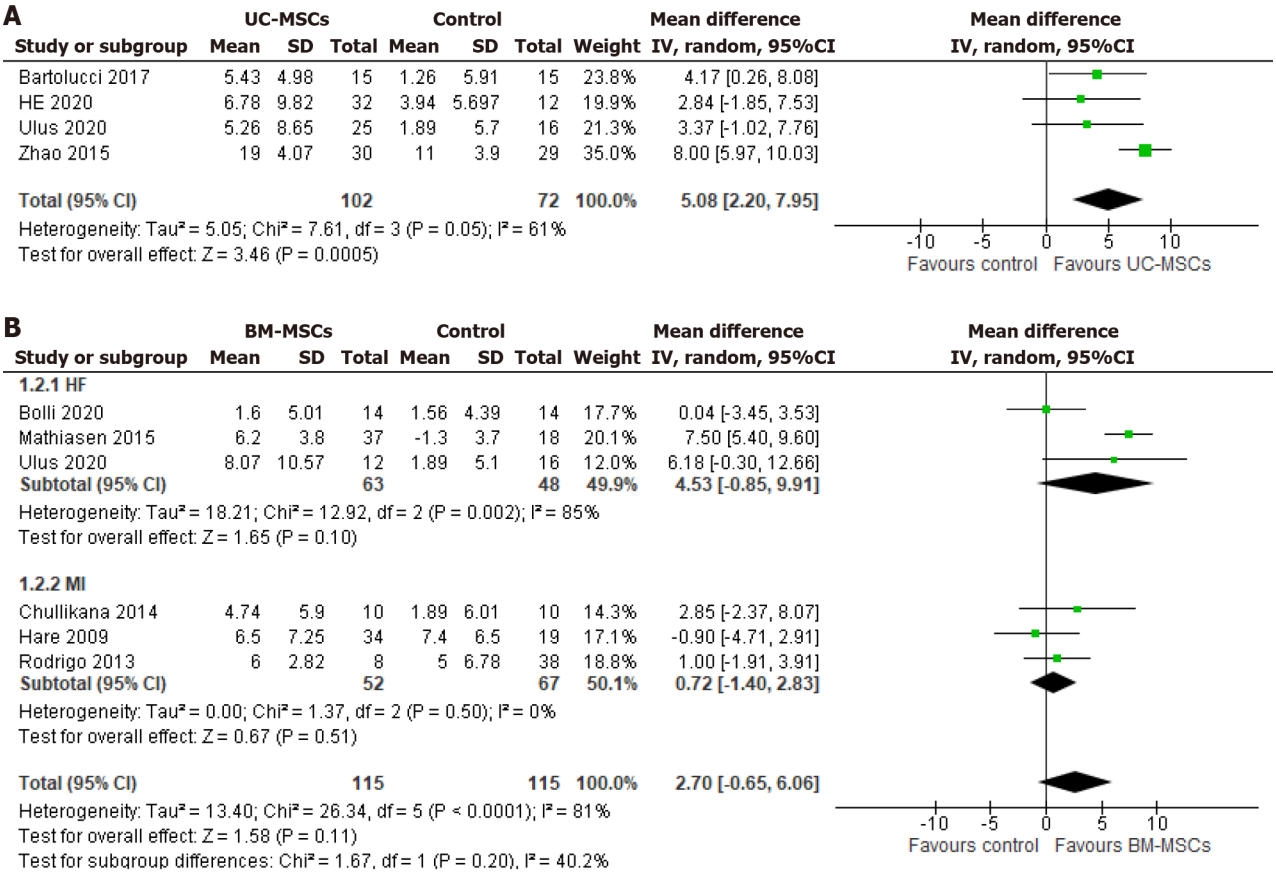


Figure 3 Forest plot of left ventricular ejection fraction change from baseline to 6 mo of follow-up. A: Umbilical-cord-derived mesenchymal stem cells; B: Bone-marrow-derived mesenchymal stem cells. UC-MSCs: Umbilical cord-derived mesenchymal stem cells; BM-MSCs: Bone marrow-derived mesenchymal stem cell; MI: Myocardial infarction; HF: Heart failure.

DISCUSSION

This systematic review and meta-analysis of MSC-based therapy evaluated the efficacy and safety of MSCs sourced from two different tissues as living biodrugs for treating CVD patients. Besides safety endpoints, the performance of the two cell types used was assessed for functional and clinical indicators, *i.e.*, LVEF and 6MWD. Our significant findings include: (1) UC-MSCs RCTs reported significant improvement in LVEF during 6 and 12 mo follow-up compared to controls and their BM-MSCs counterparts; (2) both cell types did not show a significant improvement in 6MWD compared to the baseline; and (3) both cell types exhibited no disparity in adverse events including MACEs, except for rate of rehospitalization, which showed significant reduction with BM-MSCs group compared to the UC-MSCs and control groups.

Comparing both cell types in MI and HF patients based on the above parameters, UC-MSC-treated patients had a significant pooled increase of 5.08% and 2.78% in LVEF during 6 and 12 mo follow-up, respectively, compared to the nonsignificant 2.70% and 2.14% improvement in BM-MSC-treated patients during 6 wk and 12 mo follow-up, respectively. The clinical efficacy of this intervention was evaluated through the measurement of 6MWD, an affordable, effective, and reproducible approach for assessing the physical endurance, functional capacity, and overall cardiopulmonary status of individuals with HF who do not require advanced technological equipment. After 6 mo of follow-up, only two UC-MSCs RCTs and three BM-MSCs RCTs have provided 6MWD data eligible for inclusion in the analysis. Further analysis showed no significant difference in 6MWD between intervention and control groups for either BM-MSCs or UC-MSCs.

The adverse events reported and analyzed in this review included patient mortality, rehospitalization rate, and MACEs. There was no notable disparity between the intervention and their respective control groups in the UC-MSCs and BM-MSCs RCTs, indicating the clinical safety of MSCs-based therapy. Similarly, no significant impact was observed in the UC-MSCs and BM-MSCs RCTs between the intervention and respective control groups for MACEs, which included angina, supraventricular tachycardia, ventricular tachycardia, and revascularization. Although the point estimate of the Peto OR suggested a higher incidence of MACEs in the UC-MSC group than in its control group, this difference was insignificant. The 95%CI for the Peto OR included the null value of 1.0, indicating no significant difference between the UC-MSC group and its control (95%CI: 0.42-4.60).

When analyzing the rehospitalization rates for cardiac causes following the treatment with both BM-MSCs and UC-MSCs compared to the control group, a significant 52% reduction was reported only in the BM-MSCs group. In contrast, the UC-MSCs group did not experience a significant reduction compared to the control group.

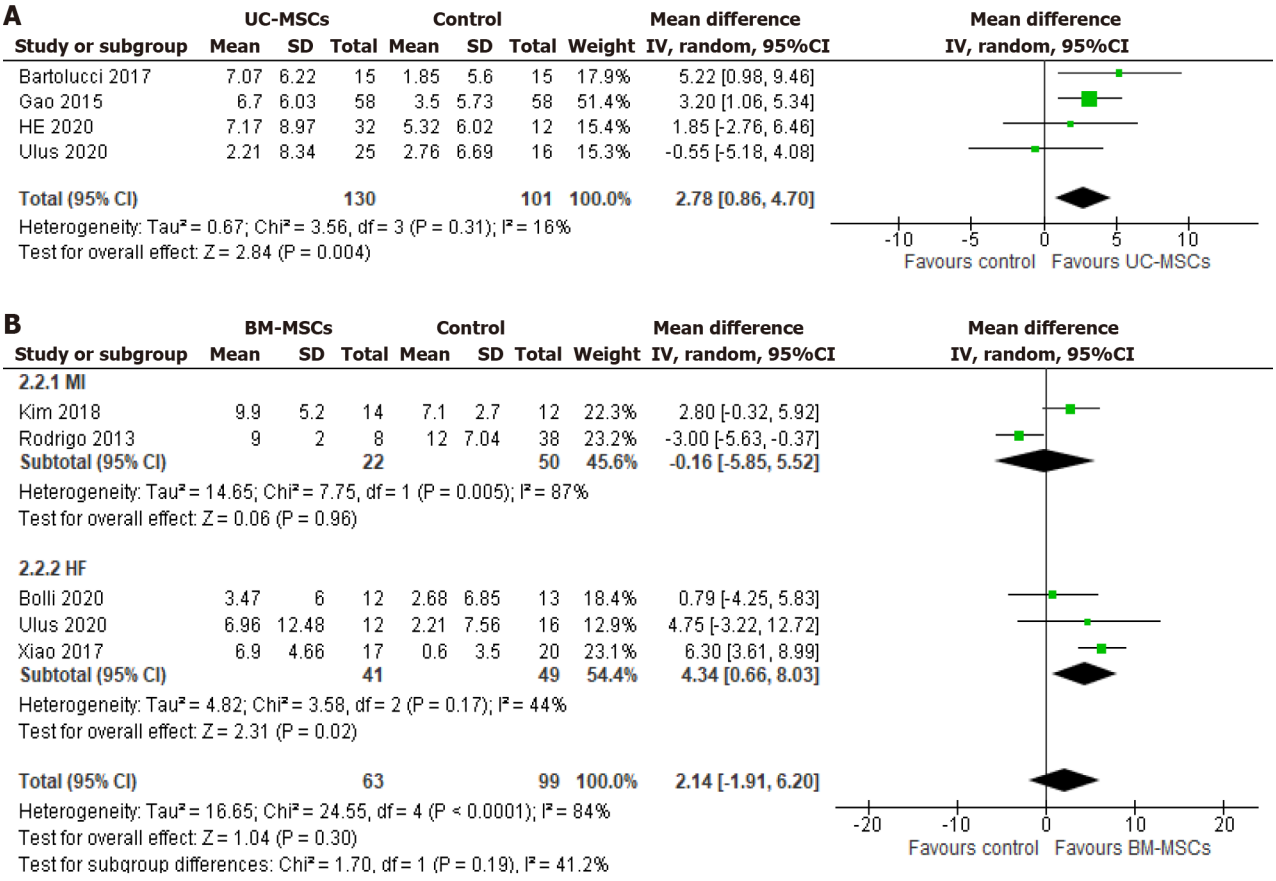


Figure 4 Forest plot of left ventricular ejection fraction change from baseline to 12 mo follow-up. A: Umbilical cord-derived mesenchymal stem cells; B: Bone marrow-derived MSCs. UC-MSCs: Umbilical-cord-derived mesenchymal stem cells; BM-MSCs: Bone-marrow-derived mesenchymal stem cell; MI: Myocardial infarction; HF: Heart failure.

A comprehensive comparison method between the two cell types was used while mitigating the impact of control group variations across studies. The means (± SDs) of the control group from the included studies of UC-MSCs and BM-MSCs were combined using Cochrane formulas, resulting in a unified control group. A similar approach was applied to the means (± SDs) of UC-MSCs and BM-MSCs derived from the included RCTs. Subsequently, each cell type's combined means (± SDs) were compared to the unified control group. This method thoroughly evaluated the effectiveness of UC-MSCs and BM-MSCs *vs* the unified control group. After applying this method, noteworthy findings emerged. Both cell types demonstrated the ability to improve LVEF at the 6-mo follow-up. However, only BM-MSCs exhibited a significant improvement at the 12-mo follow-up. While no cell type significantly affected 6MWT compared to their respective control groups, BM-MSCs demonstrated a considerable improvement compared to the unified control group. Additionally, UC-MSCs showed reduced MACE and readmission rates *vs* the unified control group. These findings highlight the significant effects of both cell types on the functional parameters of the infracted heart and patient prognosis when variations within control groups across studies were excluded.

This review focuses on phase I and II RCTs that have evaluated the safety and efficacy of MSCs derived from bone marrow and umbilical cord in patients with cardiac pathologies. The primary rationale for only including phase I and II RCTs was that all published UC-MSCs studies are limited to these early clinical trial phases. Therefore, only phase I/II RCTs utilizing BM-MSCs were incorporated to ensure a precise cell comparison.

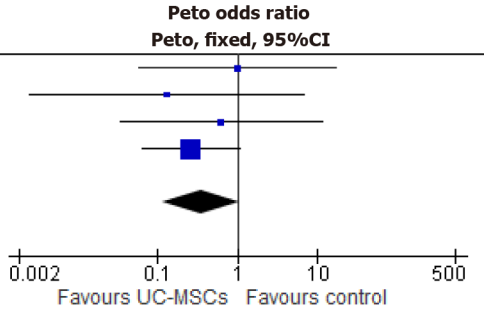
According to the data obtained from ClinicalTrials.gov, eleven ongoing RCTs investigating the use of UC-MSCs and seven RCTs studying BM-MSCs in patients with HF and MI are currently underway. These clinical trials encompass phase I to phase III.

Irrespective of the tissue source, MSCs possess low immunogenicity due to reduced expression of MHC-II molecule, lack of MHC-I expression, and the absence of co-stimulatory signals[35,36]. UC-MSCs are gaining popularity in clinical settings due to their advantages, which include noninvasive collection methods, minimal bioethical concerns, possible widespread "off-the-shelf" availability, and being rich in primitive cell populations. Additionally, like other MSC types, UC-MSCs have the added benefit of being cryopreserved for extended periods. Bárcia *et al*[36] reported successful cryopreservation of UC-MSCs using the conventional cryopreservation protocol, *i.e.*, 10% DMSO and 90% fetal bovine serum) for 3 years with a high viability rate upon thawing. Their availability without infection risk and the lack of influence from donor morbidities and aging factors put them in a position of advantage over their counterparts[37]. On the contrary, the less-than-expected results from BM-MSC-based RCTs compared to their respective control may be because most of these trials used autologous cells (Table 5). Autologous MSCs from cardiac patients are significantly affected by a plethora of comorbidities, including hypertension, diabetes mellitus, and age-related cellular changes, that

A

Study or subgroup	UC-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bartolucci 2017	1	15	1	15	15.4%	1.00 [0.06, 16.79]
Gao 2015	0	58	1	58	8.0%	0.14 [0.00, 6.82]
Ulus 2020	1	25	1	16	14.8%	0.62 [0.04, 11.07]
Zhao 2015	2	30	7	29	61.8%	0.26 [0.06, 1.08]
Total (95% CI)		**128**		**118**	**100.0%**	**0.35 [0.12, 1.06]**
Total events	4		10			

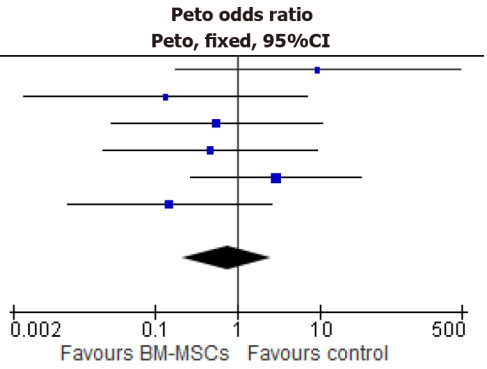
Heterogeneity: Chi² = 1.06, df = 3 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)



B

Study or subgroup	BM-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bolli 2020	1	14	0	17	9.7%	9.15 [0.18, 469.98]
Chullikana 2014	0	10	1	10	9.8%	0.14 [0.00, 6.82]
Heldman 2014	1	19	1	11	17.6%	0.55 [0.03, 10.30]
Mathiasen 2015	1	40	1	20	17.2%	0.47 [0.02, 9.05]
Ulus 2020	2	12	1	16	26.7%	2.86 [0.27, 30.76]
Xiao 2017	0	17	2	20	19.0%	0.15 [0.01, 2.50]
Total (95% CI)		**112**		**94**	**100.0%**	**0.74 [0.22, 2.54]**
Total events	5		6			

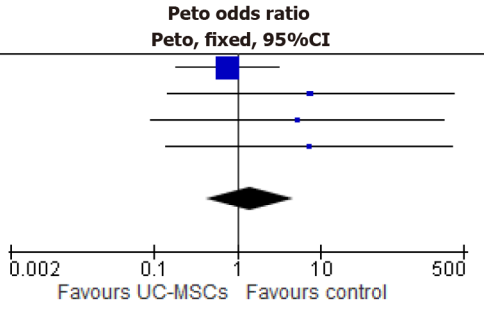
Heterogeneity: Chi² = 4.90, df = 5 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)



C

Study or subgroup	UC-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bartolucci 2017	7	15	8	15	72.4%	0.77 [0.19, 3.16]
Gao 2015	1	58	0	58	9.3%	7.39 [0.15, 372.38]
Ulus 2020	1	25	0	16	8.9%	5.16 [0.09, 286.55]
Zhao 2015	1	30	0	29	9.3%	7.15 [0.14, 360.38]
Total (95% CI)		**128**		**118**	**100.0%**	**1.39 [0.42, 4.60]**
Total events	10		8			

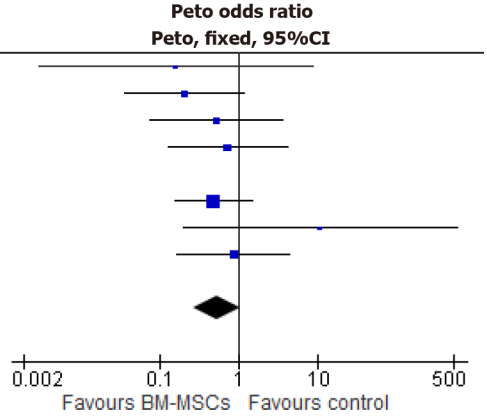
Heterogeneity: Chi² = 2.45, df = 3 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



D

Study or subgroup	BM-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bolli 2020	0	14	1	17	2.8%	0.16 [0.00, 8.29]
Chullikana 2014	4	10	8	10	14.4%	0.21 [0.04, 1.17]
Hare 2009	2	14	3	12	11.9%	0.52 [0.08, 3.51]
Heldman 2014	4	19	3	11	14.7%	0.71 [0.13, 4.02]
Kim 2018	22	34	21	19		Not estimable
Mathiasen 2015	13	40	10	20	36.7%	0.48 [0.16, 1.44]
Ulus 2020	1	12	0	16	2.8%	10.31 [0.20, 541.25]
Xiao 2017	3	17	4	20	16.6%	0.86 [0.17, 4.39]
Total (95% CI)		**160**		**125**	**100.0%**	**0.53 [0.27, 1.03]**
Total events	49		50			

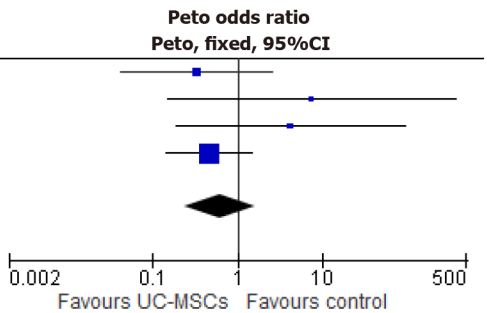
Heterogeneity: Chi² = 4.13, df = 6 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)



E

Study or subgroup	UC-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bartolucci 2017	1	15	3	15	21.0%	0.33 [0.04, 2.60]
Gao 2015	1	58	0	58	5.9%	7.39 [0.15, 372.38]
HE 2020	2	30	0	12	9.3%	4.20 [0.19, 93.78]
Zhao 2015	5	30	9	29	63.7%	0.46 [0.14, 1.51]
Total (95% CI)		**133**		**114**	**100.0%**	**0.62 [0.24, 1.60]**
Total events	9		12			

Heterogeneity: Chi² = 3.60, df = 3 (P = 0.31); I² = 17%
Test for overall effect: Z = 0.99 (P = 0.32)



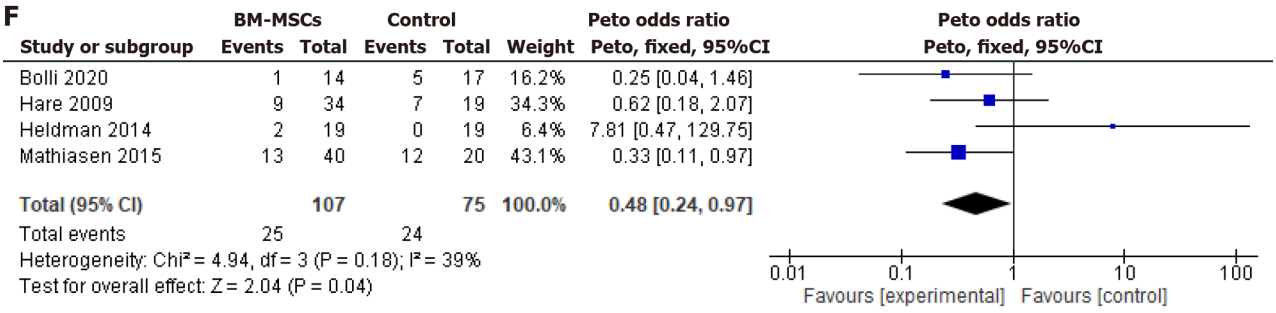


Figure 5 Forest Plot of major adverse events. A and B: Mortality in umbilical-cord-derived mesenchymal stem cells (A) and bone-marrow-derived mesenchymal stem cells (B); C and D: Major cardiac adverse events in UC-MSCs (C) and BM-MSCs (D); E and F: Rehospitalization in UC-MSCs (E) and BM-MSCs (F). UC-MSCs: Umbilical-cord-derived mesenchymal stem cells; BM-MSCs: Bone-marrow-derived mesenchymal stem cells.

compromise their therapeutic potential[10,11]. Additionally, our data showed that BM-MSCs obtained from HF patients led to a statistically significant 4.35% improvement in LVEF at the 12-mo follow-up compared to the control group. In contrast, no significant effect was observed with BM-MSCs derived from MI patients. These findings highlight the importance of the patient's clinical status in determining the therapeutic efficacy of MSC treatments.

While MSCs for cell-based therapy hold potential and have significantly affected clinical and functional study endpoints, the reported moderate improvement is also attributed to the inhospitable microenvironment in the ischemic myocardium that causes poor survival of the transplanted cells besides significantly affecting the stemness characteristics of MSCs. Various strategies are being explored, encompassing quality preconditioning of donor cells to protect them against apoptosis and ferroptosis to develop super stem cells with improved stemness and cell biology[38,39]. Based on the translational data, Xu *et al*[40] designed a multicenter phase II RCT using atorvastatin-preconditioned MSCs for patients with acute MI. This trial aimed to investigate the potential benefits of the preconditioning approach in enhancing the therapeutic effects of MSCs[40]. Additionally, optimizing cell dose and administering multiple doses of MSCs at different times may improve the outcomes[8,41].

CONCLUSION

Although RCT data from UC-MSCs in the present systematic review are encouraging, it is crucial to acknowledge that the sample size in the included studies is relatively small. Therefore, there is a need for more extensive RCTs to validate these findings. Additionally, standardization of optimal isolation and biobanking methods, time and route of administration, and cell dose are necessary for better clinical outcomes. In conclusion, our study indicated that UC-MSCs significantly improve LVEF and patient prognosis compared to their counterpart BM-MSCs. UC-MSCs may be considered a promising alternative source of MSCs for use, suggesting that they are a promising alternative for MSC-based heart therapy.

FOOTNOTES

Author contributions: Haider KH designed and produced the study and its methodology; Safwan M and Bourgleh MS performed database research and screened the extracted records against eligibility criteria; Bourgleh MS, Aldoush M, and Safwan M performed the data extraction and plotting; Safwan M and Aldoush M reviewed and validated the extracted data; Safwan M and Bourgleh MS performed the quality assessment of the included trials; Bourgleh MS and Safwan M conducted the statistical analysis; Safwan M and Haider KH drafted the first manuscript; All the authors contributed to the final manuscript, reviewed the final manuscript and have read and agreed to the published version of the manuscript.

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CASE REPORT

Unloading and successful treatment with bioresorbable stents during percutaneous coronary intervention: A case report

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Abstract

BACKGROUND

With the development of percutaneous coronary intervention (PCI), the number of interventional procedures without implantation, such as bioresorbable stents (BRS) and drug-coated balloons, has increased annually. Metal drug-eluting stent unloading is one of the most common clinical complications. Comparatively, BRS detachment is more concealed and harmful, but has yet to be reported in clinical research. In this study, we report a case of BRS unloading and successful rescue.

CASE SUMMARY

This is a case of a 59-year-old male with the following medical history: "Type 2 diabetes mellitus" for 2 years, maintained with metformin extended-release tablets, 1 g PO BID; "hypertension" for 20 years, with long-term use of metoprolol sustained-release tablets, 47.5 mg PO QD; "hyperlipidemia" for 20 years, without regular medication. He was admitted to the emergency department of our hospital due to intermittent chest pain lasting 18 hours, on February 20, 2022 at 15: 35. Electrocardiogram results showed sinus rhythm, ST-segment elevation in leads I and avL, and poor R-wave progression in leads V1–3. High-sensitivity troponin I level was 4.59 ng/mL, indicating an acute high lateral wall myocardial infarction. The patient's family requested treatment with BRS, without implanta-

tion. During PCI, the BRS became unloaded but was successfully rescued. The patient was followed up for 2 years; he had no episodes of angina pectoris and was in generally good condition.

CONCLUSION
We describe a case of a 59-year-old male experienced BRS unloading and successful rescue. By analyzing images, the causes of BRS unloading and the treatment plan are discussed to provide insights for BRS release operations. We discuss preventive measures for BRS unloading.

Key Words: Coronary artery diseases; Percutaneous coronary intervention; Bioresorbable stents; Stent unloading; Stent release; Intravascular ultrasound; Case report

Core Tip: Percutaneous coronary intervention plays a vital role in the treatment of coronary artery diseases. Recently, considerable attention has been given to bioresorbable stents (BRS), which can relieve coronary artery occlusions and reduce vascular stenosis. BRS can be absorbed or degraded, which helps restore vascular endothelial function and normalize systolic and diastolic functions. However, reports of clinical cases of BRS-unloading have been limited. Here, we present a case of BRS unloading and successful rescue, providing a practical treatment plan for such clinical scenarios.

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INTRODUCTION

Percutaneous coronary intervention (PCI) plays a vital role in the treatment of coronary artery diseases. Recently, considerable attention has been given to bioresorbable stents (BRS); these can relieve coronary artery occlusion, reduce vascular stenosis, be absorbed or degraded, restore vascular endothelial function, and normalize systolic and diastolic functions. However, only a few publications have discussed clinical cases of BRS unloading.

CASE PRESENTATION

Chief complaints

The patient was a 59-year-old male admitted to the emergency department of our hospital at 15: 35 on February 20, 2022, due to intermittent chest pain for 18 hours.

History of present illness

The patient was a 59-year-old male admitted to the emergency department of our hospital at 15: 35 on February 20, 2022, due to intermittent chest pain for 18 hours. Electrocardiogram (ECG) results showed sinus rhythm, ST-segment elevation in leads I and avL, and poor R-wave progression in leads V1–3. High-sensitivity troponin I (hs-TnI) level was at 4.59 ng/mL, indicating an acute high lateral wall myocardial infarction. The patient refused emergency PCI treatment as the chest pain had been relieved; therefore, he was transferred to the Department of Cardiology.

History of past illness

He had the following medical history: "Type 2 diabetes mellitus" for 2 years, maintained with metformin extended-release tablets, 1 g PO BID; "hypertension" for 20 years, with long-term use of metoprolol sustained-release tablets, 47.5 mg PO QD; "hyperlipidemia" for 20 years, without regular medication.

Personal and family history

He denied a history of smoking and had no family history of related disease.

Physical examination

Admission examination: Temperature: 36.5 °C, Pulse: 75 beats/min, Respiration: 18 breaths/min, Blood Pressure: 138/74 mmHg (1 mmHg = 0.133 kPa), clear breath sounds in both lungs, no dry or wet rales, normal heart boundaries, heart rate 75 beats/min, regular rhythm, and no pathological murmur.

Laboratory examinations

The ECG results showed sinus rhythm, ST-segment elevation in leads I and avL, and poor R-wave progression in leads V1–3 (Figure 1). hs-TnI level was at 4.59 ng/mL. N-terminal pro-brain natriuretic peptide levels were normal upon admission.

Imaging examinations

Echocardiography revealed abnormal left ventricular wall motion, mild mitral regurgitation, tricuspid and aortic valves, and a left ventricular ejection fraction of 62%.

FINAL DIAGNOSIS

(1) Acute high lateral myocardial infarction of coronary heart disease, cardiac function class I (Killip classification); (2) Hypertension grade 3, very high risk; and (3) Type 2 diabetes mellitus.

TREATMENT

Upon admission, the patient was administered aspirin and clopidogrel for dual antiplatelet therapy, heparin for anticoagulation, and atorvastatin for lipid reduction. Coronary angiography was performed on the second day, revealing a dominant left coronary artery. Other findings were as follows: Non-stenotic left main artery, 85% stenosis in the proximal and middle segments of the anterior descending artery, 50% stenosis in the middle and distal segments of the circumflex artery, and 75% stenosis in the proximal segment of the right coronary artery (Figures 2 and 3). The patient's family requested treatment with BRS without implantation. Because there was no stock in the catheter room, interventional treatment of the left anterior descending artery (LAD) was postponed until the fourth day. The 6F SPB 3.5 guiding catheter was sent along the sheath to connect the left coronary ostia, while the Rinato and Sion Blue guidewires were sent through the catheter to the LAD and distal segment of the first diagonal branch.

Intravascular ultrasound (IVUS) examination showed that the middle segment of the LAD was the myocardial bridge; diffused low-to-moderate echogenic plaques were observed in the lumen from the middle segment, close to the myocardial bridge to the ostium of the LAD. The minimum lumen area of the proximal segment was 1.85 mm^2, with mild local calcification (Figure 3). The 2.0 mm × 20 mm semi-compliant, 2.75 mm × 12 mm non-compliant, and 2.75 mm × 10 mm cutting balloons were used multiple times for pre-expansion at 6-10 atm at the lesion in the proximal and middle segments of the LAD; angiography showed a satisfactory expansion effect (Figure 4A). Subsequently, the first BRS, measuring 3.0 mm × 18 mm, was implanted at 12 atm in the proximal middle segment of the LAD, avoiding the myocardial bridge. A second BRS, measuring 3.5 mm × 18 mm, was also delivered along the Rinato guidewire to the lesion of the proximal part of the LAD.

During the positioning process, the patient suddenly coughed. Consequently, the guiding catheter was inserted deeply into the proximal segment of the LAD with the BRS. The positions of the guiding catheter and BRS were then promptly adjusted. The appearance of "smoke" indicated a significant worsening of the lesions in the proximal segment and ostium of the LAD compared to the previous state (Figures 4B and 5). Considering the potential risk of local hematoma or dissection, we immediately withdrew the BRS and sent it to IVUS for detection; the results indicated that the BRS was unloaded. The distal end of the second BRS was positioned close to the afflux of the first diagonal branch. The proximal end intruded approximately 2 mm into the left main stem (Figure 5). The 2.0 mm × 20 mm semi-compliant balloons; and the 2.75 mm × 12 mm, 3.0 mm × 12 mm, and 3.5 mm × 12 mm non-compliant balloons, were sent along the Rinato guidewire into the second BRS and expanded at 6-12 atm for immediate in-situ release. IVUS revealed poor adherence at the proximal end of the BRS. Subsequently, a 4.0 mm × 12 mm non-compliant balloon was delivered into the BRS at the end of the left main stem and ostium of the LAD, which was then post-dilated at 14 atm. IVUS detection indicated that the structure of the BRS was complete and adherent. There was an approximately 2 mm gap between the two BRS at the LAD near the afflux of the first diagonal branch, without dissection or hematoma formation. The minimum lumen area was 5.26 mm^2 (Figure 6); angiography confirmed completely patent blood vessels with thrombolysis in TIMI grade 3 distal blood flow (Figure 4C).

OUTCOME AND FOLLOW-UP

Immediate IVUS evaluation was satisfactory. The patient was followed up for 2 years, having no episodes of angina pectoris and with generally good condition.

DISCUSSION

Emergency or elective PCI can relieve coronary artery occlusion or stenosis, and is one of the most effective methods for treating coronary heart diseases. BRS is a significant advancement in stent technology; it can achieve complete

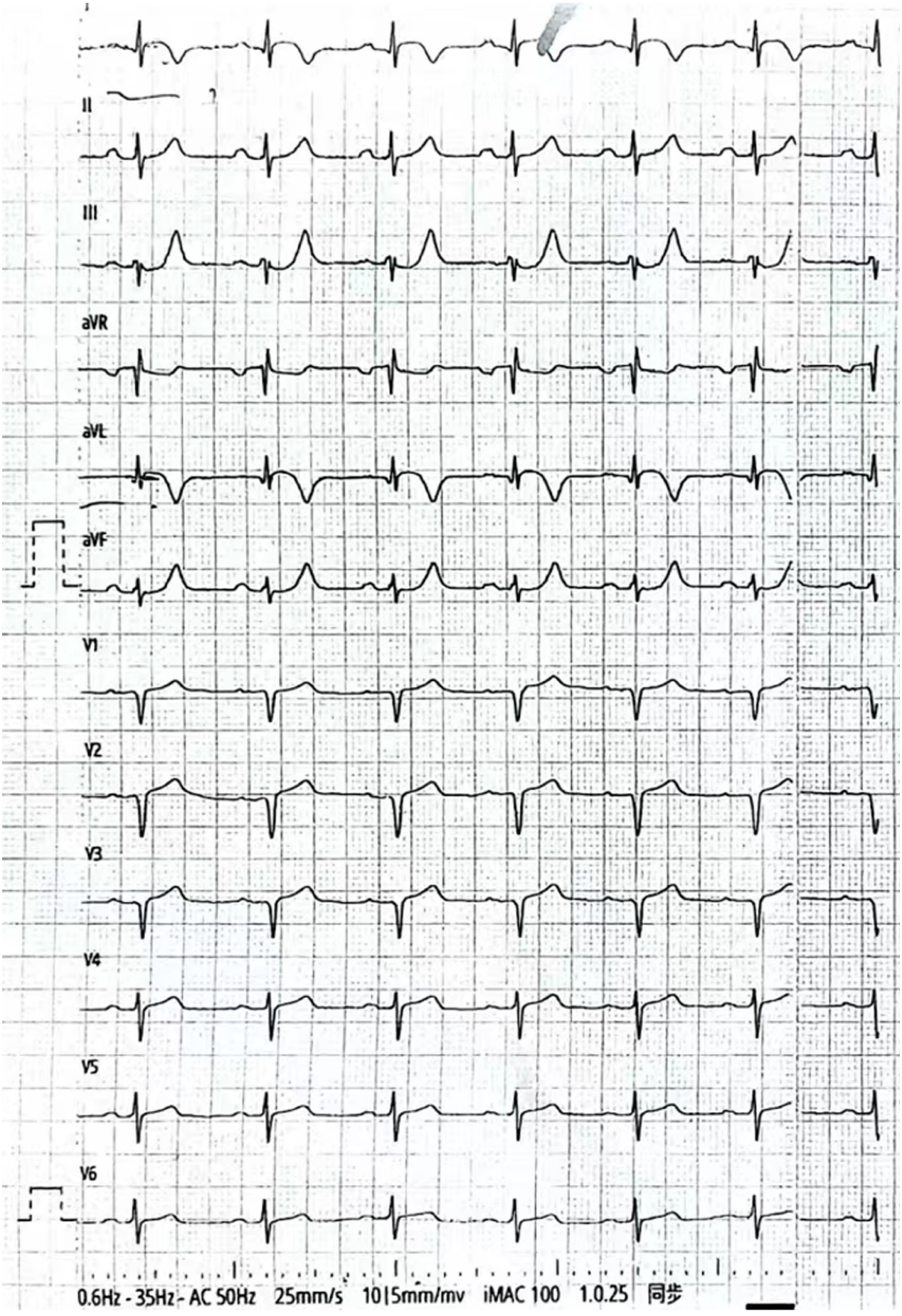

Figure 1 Electrocardiogram examination on admission.

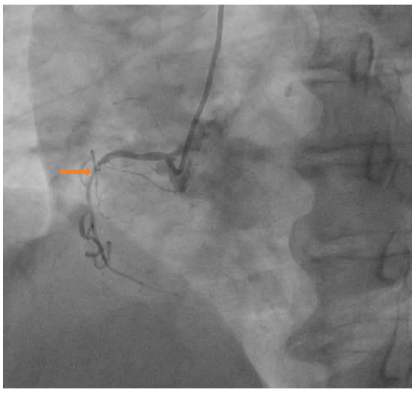

Figure 2 Preoperative images. Right coronary angiography (Left anterior position).

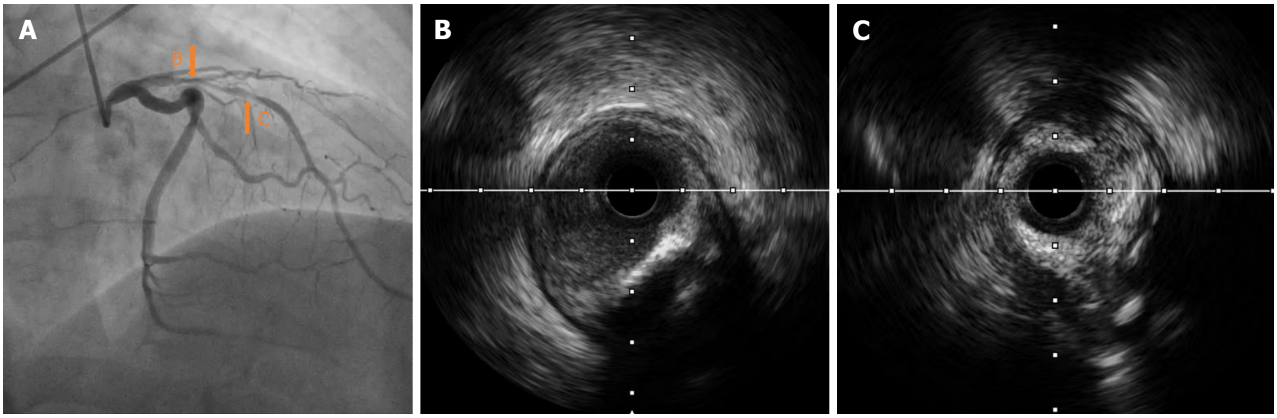

Figure 3 Preoperative images. A: Left coronary angiography (right shoulder position); B: Intravascular ultrasound (IVUS) of the proximal segments of the left anterior descending artery (LAD); C: IVUS of the middle segments of the LAD.

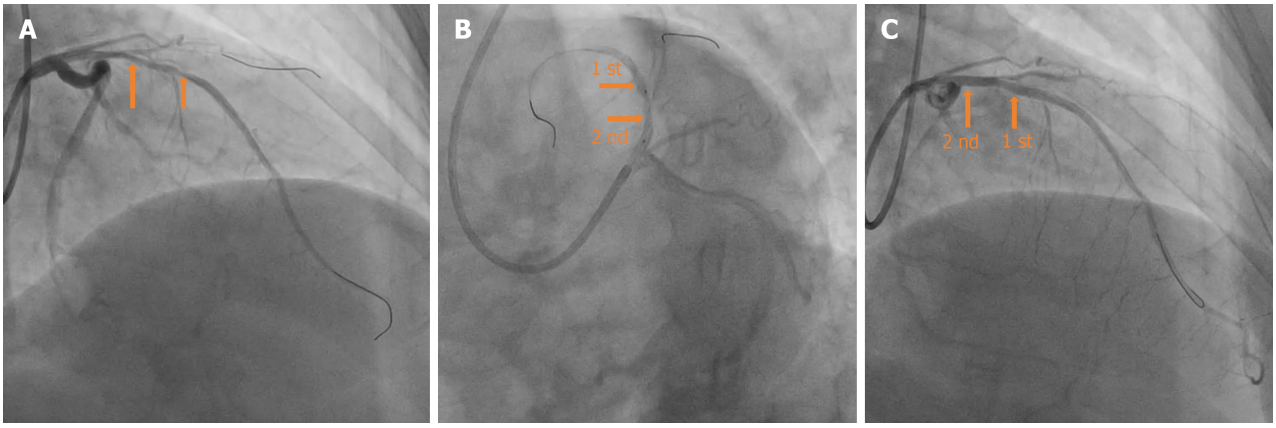

Figure 4 Intraoperative stent position. A: Angiography (right shoulder position) after balloon dilation of the proximal and middle segments of the left anterior descending artery; B: Angiography (spider position) Positioning of the second bioresorbable stents (BRS) after the first BRS implantation in the middle descending artery; C: Postoperative images after BRS *in situ* expansion from proximal segment to left main trunk in the right shoulder position.

degradation of stents, restoration of blood vessels elasticity, and promotion of the normal blood vessel structure and function recovery[1,2]. While DES unloading is a known iatrogenic complication of PCI, few clinical cases of BRS detachment have been reported. Common causes of DES unloading include[3]: Pathological factors such as moderate to severe calcification, severe angulation, or distortion; device-related factors include using a smaller guiding catheter, misalignment of the guiding catheter and blood vessel axes, scratch on the extended catheter, and loose kneading of the stent and balloon; technical operation factors such as inadequate pretreatment.

In this case, the lesion had mild local calcification; the effect of angiographic evaluation after balloon pretreatment was acceptable. Furthermore, BRS unloading may be due to an unstable intraoperative guiding catheter, thus resulting in BRS

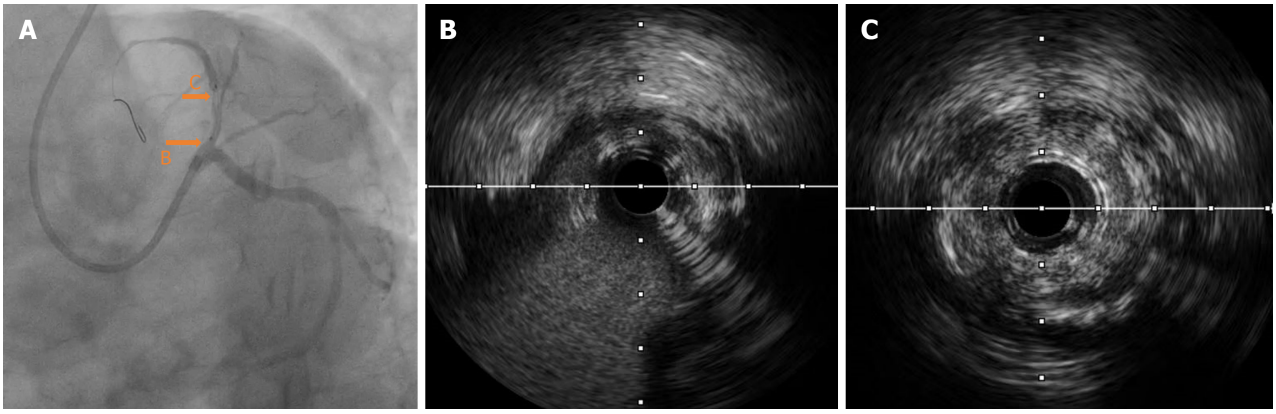

Figure 5 Angiography (spider position). A: Imaging changes in the proximal segment of the left anterior descending artery; B: Intravascular ultrasound (IVUS) of the proximal end of the unloaded bioresorbable stents (BRS) stent; C: IVUS of the distal end of the unloaded BRS stent.

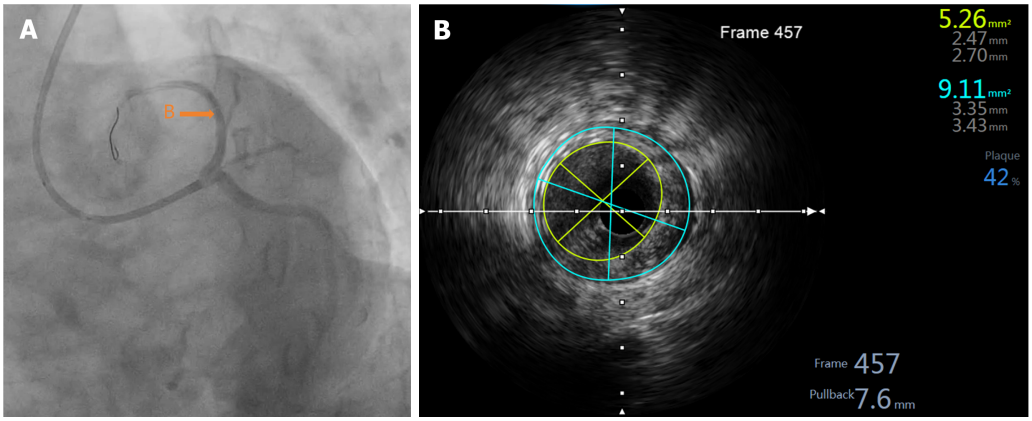

Figure 6 Postoperative images. A: After bioresorbable stents *in situ* expansion from proximal segment to left main trunk: In the spider position; B: Intravascular ultrasound of the proximal of left anterior descending artery after bioresorbable stents expansion: The minimum lumen area was 5.26 mm².

scratching and reduced scaffold balloon adhesion; therefore, the BRS was completely separated from its stent balloon during PCI. Prevention of stent unloading is far more important than treatment; comprehensive preoperative lesion evaluation, formulation of a PCI strategy, selection of an appropriate guiding catheter, and good coaxial and gentle operations are indispensable. Because the lateral beam of BRS is thicker than that of DES, adequate pretreatment should be performed before BRS implantation. PSP operation[4] guarantees successful implantation and reduces poor BRS expansion.

In addition, precautions should be taken to prevent BRS unloading. Once the BRS is in place, operators should strive for a single release to prevent repetitive insertion and removal. In this case, the BRS is made of polylactic acid; its stress-relaxation properties have obvious temperature sensitivity[5]. The body temperature affects the adhesion performance between the scaffold balloon and stent during delivery. Therefore, it needs to be released as soon as possible. The resistance increases and the sense of loss occurs when DES is unloaded; however, BRS unloading differs from DES unloading in terms of hand-feeling. BRS features a thicker lateral wall that is susceptible to scratching. When unloading occurs, the operator may not feel it in his hands; X-ray fluoroscopy and angiography are not easy to find in time. Therefore, caution is warranted during PCI. During BRS localization, the possibility of stent unloading should be considered when coronary angiography reveals imaging changes, especially when the original coronary artery lesion seems to be aggravated. This is because the thickness of the unloaded BRS side wall overlaps with that of the original lesion, which leads to a change in contrast agent filling. Therefore, the BRS should not be withdrawn or immediately released for evaluation.

This study has limitations. There were differences between the treatments with unloaded BRS and DES. The use of a stent to crush an unloaded BRS into the vessel wall is inappropriate. First, it is difficult to crush thick biodegradable materials onto vessel walls to ensure adhesion. Second, the mural cavity formed after material degradation can easily lead to an increased risk of thrombosis. Because the BRS material is not radiopaque, X-rays can hardly detect it, making it very difficult to remove the unloaded BRS from the body. In this case, BRS unloading was found at the lesion site on IVUS examination, and was rescued by local release. Immediate IVUS evaluation was satisfactory. The outpatient was followed up for 2 years, having no episodes of angina pectoris and with generally good condition.

CONCLUSION

We report a case of BRS unloading and successful rescue, and provide a practical treatment plan for clinical BRS unloading. In the future, we plan to conduct research to completely prevent its occurrence.

FOOTNOTES

Author contributions: Sun T and Zhang MX contribute equally to this study as co-first authors. Zhu HM and Long Y contribute equally to this study as co-corresponding authors; Sun T and Zhang MX reviewed the literature and contributed to manuscript drafting; Zeng Y was the patient's cardiovascular doctor and interpreted the imaging findings; Ruan LH, Yang CL, and Qin Z analyzed and interpreted the imaging findings; Wang J reviewed the literature; Zhu HM and Long Y was responsible for revising the manuscript and for providing intellectual contributions; all authors approved the final version to be submitted.

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CASE REPORT

Antiphospholipid syndrome presenting as recurrent coronary thrombosis: A case report

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Abstract

BACKGROUND

Antiphospholipid syndrome (APS) is a chronic autoimmune disease characterized by venous or arterial thrombosis, pregnancy morbidity and a variety of other autoimmune and inflammatory complications. Here, we report a case of APS associated with multiple coronary thromboses.

CASE SUMMARY

The patient, a 28-year-old male, suffered from recurrent coronary thromboses over a period of 31 months. Despite undergoing interventional coronary procedures, thrombolytic therapy, and anticoagulation treatment, the condition persisted intermittently. An extensive search for underlying thrombogenic factors revealed a diagnosis of APS. Accurate adjustment of the medication regimen led to the absence of further acute coronary syndrome (ACS) episodes during the subsequent 20-month follow-up. Although the patient occasionally experiences chest tightness, no further symptoms of distress have been reported.

CONCLUSION

APS can manifest as ACS. Screening for rheumatologic and immunological conditions is essential when encountering patients with multiple coronary thromboses. Treatment strategy should include symptomatic relief and a targeted and aggressive approach to address the underlying pathophysiology.

Key Words: Antiphospholipid syndrome; Acute coronary syndrome; Coronary angiography; Lupus anticoagulant; Treatment for antiphospholipid syndrome; Case report

Core Tip: Antiphospholipid syndrome (APS) is primarily identified by its thrombotic phenomena. Thus, healthcare professionals should be highly vigilant for the assorted clinical symptoms that can stem from thromboembolic events, which have the potential to involve several organ systems. When encountering young individuals with frequent angina attacks who do not possess conventional risk factors, it is imperative not to pinpoint the cause solely on cardiac issues. The integration of percutaneous coronary intervention and specific treatment targeting the etiology of APS is essential. The need to preserve a heightened awareness of the spectrum of clinical signs linked to thromboembolic complications affecting diverse organ systems is required.

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INTRODUCTION

Antiphospholipid syndrome (APS) is a thromboinflammatory disease that complicates up to one third of cases of systemic lupus erythematosus, which may result in more organ damage over time. APS is most prominently characterized by thrombotic manifestations, such as common deep vein thrombosis, cerebral artery thrombosis, and so on[1]. Studies have suggested that the presence of lupus anticoagulant is more strongly associated with an increased risk of thromboembolic episodes than the detection of positive anti-cardiolipin antibodies[2]. Primary APS can also occur in the absence of other systemic autoimmune disorders. Acute coronary syndrome (ACS) refers to a spectrum of coronary artery pathologies, including unstable angina, non-ST segment elevation myocardial infarction and ST-segment elevation myocardial infarction, and its common manifestations include chest pain[3]. In clinical settings, patients with APS often present with a predominant thrombotic phenotype, which complicates the distinction between their symptoms and those associated with ACS, leading to diagnostic challenges.

CASE PRESENTATION

Chief complaints

The patient, a 28-year-old male, was admitted to the hospital with a history of paroxysmal chest tightness spanning approximately 31 months.

History of present illness

Thirty-one months ago, the patient experienced a sudden onset of chest discomfort, accompanied by difficulty breathing and diaphoresis, which was subsequently diagnosed as "acute ST segment elevation myocardial infarction" affecting both the anterior and inferior walls following electrocardiogram and cardiac biomarker assessments at a local hospital. Coronary angiography revealed occlusion of the proximal left anterior descending (LAD) coronary artery and complete occlusion at the posterior opening of the right coronary artery (Figure 1A). Interventional treatment included stent implantation in the LAD and percutaneous transluminal coronary angioplasty in the right coronary artery. After discharge, the patient maintained a regimen of antiplatelet and anticoagulant medications. A follow-up examination two weeks later showed thrombosis in the LAD, which was again relieved by balloon dilation (Figure 1B). Initial screening for lupus anticoagulants was positive, with an increased ratio of lupus anticoagulant initial screening to confirmation (LA1/LA2) of 1.39, indicating a low level of lupus anticoagulants, but no specific treatment was initiated. Two years ago, the patient presented to our hospital with recurrent chest tightness. Coronary angiography revealed thrombus formation within the LAD stent. Balloon dilation of the LAD and laser treatment of the right coronary artery were performed (Figure 1C). The initial lupus anticoagulant screening was again positive, with a slightly increased LA1/LA2 ratio of 1.23. In addition to the ongoing antiplatelet and anticoagulant therapy, hydroxychloroquine 100 mg twice daily was added to the treatment regimen. Six months ago, the patient experienced another episode of chest tightness, prompting a repeat coronary angiography, which showed occlusion of the LAD stent (Figure 1D), necessitating another balloon dilation treatment. Based on the APS diagnostic criteria and the patient's clinical presentation, a diagnosis of APS was confirmed.

History of past illness

The patient's medical history was remarkable by the recurrence of thrombotic episodes. Five years previously, the patient experienced an acute episode of dyspnea, and underwent pulmonary computed tomography angiography, which diagnosed bilateral pulmonary artery embolism. Concurrently, venous thrombosis was identified in the right superficial femoral, popliteal, anterior tibial, and posterior tibial veins. Approximately four and a half years ago, the patient subsequently developed additional thrombosis in the right popliteal and intermuscular veins of the lower leg.

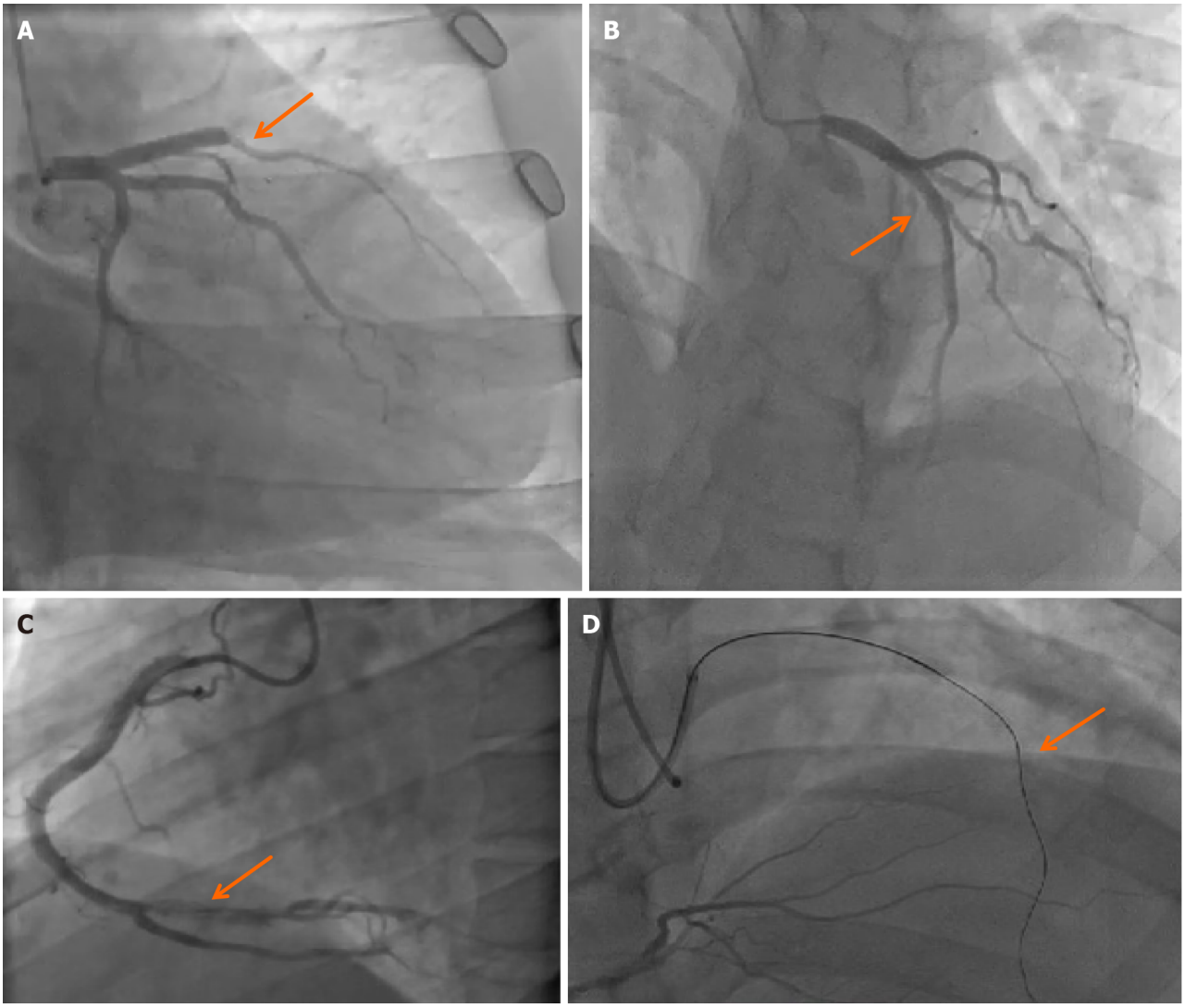

Figure 1 Coronary angiography images. A: Stenosis of the left anterior descending (LAD) coronary artery; B: Stenosis of the left circumflex coronary artery; C: Thrombosis of the right coronary artery branch to back of the left ventricle; D: Complete occlusion of the LAD artery.

Personal and family history

The patient had a 10-year history of smoking, with an average consumption of 10 cigarettes daily, and occasionally indulges in alcohol. He did not have a family history of cardiovascular disease.

Physical examination

The patient's body temperature was 36.5 °C, pulse rate was 69 beats/min, respiratory rate was 18 breaths/min and blood pressure was 98/69 mmHg. The patient was alert and oriented. Auscultation of the lungs revealed clear breath sounds with the absence of dry or wet rales. The heart rate was 69 beats/min and maintained a regular rhythm; no appreciable murmurs were detected in the valve areas. Abdominal examination was unremarkable, with no tenderness or rebound pain, and the liver and spleen were non-palpable. No edema was noted in the lower extremities. The admission electrocardiogram showed the presence of Q waves in leads V1 through V5.

Laboratory examinations

Thirty-one months ago, initial screening for lupus anticoagulants was positive, with an increased LA1/LA2 ratio of 1.39, indicating a low level of lupus anticoagulants. Two years ago, the initial lupus anticoagulant screening was again positive, with a slightly increased LA1/LA2 ratio of 1.23. Six months ago, the LA1/LA2 ratio improved to 1.31.

Imaging examinations

Thirty-one months ago, coronary angiography revealed occlusion of the proximal LAD coronary artery and complete occlusion at the posterior opening of the right coronary artery. A follow-up examination two weeks later showed thrombosis in the LAD. Two years ago, coronary angiography revealed thrombus formation within the LAD stent. Six months ago, repeat coronary angiography showed occlusion of the LAD stent, and echocardiography revealed a thrombus at the left ventricular apex.

FINAL DIAGNOSIS

The diagnoses were APS, coronary artery thrombosis, coronary atherosclerotic heart disease, old extensive anterior and inferior wall myocardial infarction, and heart function Class II (NYHA).

TREATMENT

In addressing the coronary artery occlusion, the patient underwent balloon angioplasty as a therapeutic intervention. Concurrent with the diagnosis of APS, the patient's treatment regimen included hydroxychloroquine, warfarin for anticoagulation purposes, indobufen as an antiplatelet agent, and rosuvastatin to reduce blood lipid levels and promote plaque stabilization.

OUTCOME AND FOLLOW-UP

The patient has experienced a marked reduction in chest pain symptoms compared to his previous condition. Accurate adjustment of the medication regimen led to the absence of further ACS episodes throughout the subsequent 20-month follow-up. While the patient may occasionally suffer from a sensation of chest constriction, there have been no additional reports of distressing symptoms.

DISCUSSION

Clinical diagnostic criteria for APS are: One or more episodes of thrombosis are present in arteries, veins, or small blood vessels of any organ or tissue (excluding superficial venous thrombosis as a diagnostic marker). Objective evidence, such as imaging or histopathological findings, is required. In cases where histopathology confirms thrombosis, the vessel walls at the site of the thrombus must exhibit no signs of vascular inflammation. Laboratory diagnostic criteria in terms of lupus anticoagulant level in plasma are: The level must be tested at a minimum interval of 12 weeks between tests, and the result should be positive on at least two separate occasions. For a diagnosis of APS, the positive antiphospholipid antibody test result should not be less than 12 weeks before or more than 5 years after the onset of clinical symptoms[4, 5]. In the present case, based on the patient's clinical presentation and auxiliary diagnostic examinations, which align with the aforementioned criteria, the diagnosis of APS is established.

The distinctive aspect of this case is the patient's profile: A young male without conventional risk factors for coronary heart disease, such as hypertension, diabetes, hyperlipidemia, advanced age, or a family history of genetic disorders. Despite this, the patient has experienced repeated thrombotic events across multiple vascular beds, including the deep veins of the lower limbs, coronary arteries, pulmonary arteries, and the left ventricle. The clinical presentation of cardiovascular diseases alone fails to adequately explain the patient's symptoms. Furthermore, the patient's history of multiple emboli is not confined to the lower limb veins but is more significantly manifested in the coronary arteries. The negative results for anticardiolipin antibodies and anti-β2-glycoprotein I antibodies, coupled with the patient's cardiac symptoms, add to the diagnostic complexity and challenge. This case underscores the importance of looking beyond superficial symptoms and considering a broader range of diseases, including those related to the rheumatic and immune systems, in the diagnostic process. The significance of this case lies in its potential to inform a diagnostic and therapeutic approach for clinicians faced with similar presentations, enabling earlier diagnosis and treatment and preventing the progression of complications and adverse outcomes. Considering the proneness of APS patients to thrombosis and a hypercoagulable state, it is imperative to investigate optimal personalized treatment strategies for APS patients with ACS.

CONCLUSION

The clinical features of APS are predominantly marked by thrombotic events. It is crucial to maintain a high index of suspicion for the varied clinical manifestations that can result from thromboembolic complications affecting multiple organ systems. In young patients who lack traditional risk factors for coronary atherosclerosis and who suffer from recurrent episodes of angina, it is imperative not to limit the diagnostic focus solely to cardiac pathologies. Instead, the possibility of APS should also be actively considered in the differential diagnosis. In light of the heightened risk of thrombosis and the hypercoagulable state inherent in patients with APS, there is an urgent call for additional research and advancement to delineate the most effective personalized percutaneous coronary intervention treatment protocols for APS patients who are diagnosed with ACS.

FOOTNOTES

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