Nitta and Kinugawa
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REVIEW

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Diagnosis and treatment of heart failure with preserved ejection fraction in patients on hemodialysis

Kosaku Nitta[1*] and Koichiro Kinugawa[2]

Abstract

Heart failure (HF) is a frequent complication and the main cause of death in patients on dialysis. HF with preserved ejection fraction (HFpEF) is a complicated syndrome that manifests as diastolic dysfunction and increased left ventricular filling pressure. Few studies have investigated HFpEF in dialysis patients, so the diagnosis and treatment of HFpEF remains challenging. The recently published the Japanese Circulation Society (JCS)/the Japanese Heart Failure Society (JHFS) 2021 guidelines have reported a new diagnostic procedure for HF. In dialysis patients, HF is typically observed as left ventricular diastolic dysfunction in association with HFpEF. Recent reports have shown that risk factors for HF in dialysis patients include not only traditional risk factors, such as age, smoking, obesity, hypertension, dyslipidemia, and diabetes, but also nontraditional risk factors such as fluid overload, renal anemia, disorders of calcium and phosphate metabolism, uremic toxins, and malnutrition. In the management of dialysis patients, volume control is important for controlling intradialytic hypotension, which is associated with higher mortality. Also, adequate pharmacological treatment of HFpEF is difficult in these patients, so a robust protocol developed for non-dialysis patients with HFpEF may be useful for treating patients on dialysis. This review explores the characteristics of hemodialysis patients with HFpEF and diagnostic and treatment procedures for these patients.

Keywords Heart failure with preserved ejection fraction, Hemodialysis, Diagnostic procedure, Treatment

Introduction

The population of patients on dialysis continues to grow globally in conjunction with population aging, and the management of these patients poses various challenges in terms of complications and mortality. According to the Japanese Society for Dialysis Therapy (JSDT), the annual all-cause mortality of patients on chronic dialysis in Japan was 9.9% in 2020 [1]. The relatively low rate indicates that the life expectancy of Japanese dialysis patients is among the highest in the world, even as the average age of these patients is increasing. Nonetheless, in dialysis patients, mortality due to infectious diseases has recently increased and cardiovascular disease (CVD) remains a major concern, accounting for 40% of all deaths. In particular, the Statistical Survey Committee of JSDT has reported that heart failure (HF) was the most common cause of death, accounting for 25% of all-cause mortality in these patients. About 20% of hemodialysis patients experience HF with reduced ejection fraction (HFrEF) according to clinical examinations and echocardiographic studies [2, 3]. Advances have been made in therapeutic strategies for HF, such as antihypertensive drugs and treatment of anemia and chronic kidney disease, mineral and bone disorder (CKD–MBD), but the

*Correspondence:
Kosaku Nitta
nitta.kosaku@gmail.com
[1] Department of Nephrology, Tokyo Women's Medical University, 8-1 Kawada-Cho, Shinjuku-Ku, Tokyo 162-8666, Japan
[2] Second Department of Internal Medicine, University of Toyama, Toyama, Japan

management of CVD including HF remains as an important clinical problem to be addressed [4]. One challenge is that structural and functional abnormalities of the heart are more common reported more often in dialysis patients than in non-dialysis patients. Another is that, volume expansion often occurs in dialysis patients, which can exacerbate hypertension and induce left ventricular (LV) hypertrophy. HF in dialysis patients is mainly manifested as LV diastolic dysfunction with preserved ejection fraction, termed as heart failure with preserved ejection fraction (HFpEF) [5]. Nevertheless, HFpEF has been inadequately recognized, because past researches largely focused on HFrEF. In this review, we give an overview of HFpEF in hemodialysis patients, associated biomarkers and diagnostic procedures, and the therapeutic management of these patients.

Classification of HF preserved or reduced ejection fraction

HF is a complicated syndrome that causes various symptoms, including fatigue, dyspnea, and edema, as well as reduced exercise tolerance as a result of decompensated cardiac pumping function due to structural and functional disorders of the heart (Table 1). The recent JCS/JHFS 2021 guidelines [6] divide patients with HF into three groups (Table 2) based on the severity of LV impairment: HFrEF, LV ejection fraction (LVEF) < 40%; HF with mildly reduced EF (HFmrEF), LVEF of 40-% to < 50%; and HFpEF, LVEF > 50% with objective evidence of structural or functional abnormalities of the heart that are consistent with diastolic dysfunction or elevated filling pressures, including increases in brain natriuretic peptide (BNP) and its inactive N-terminal fragment (NT-proBNP) [6].

Cardiac background in dialysis patients

Dialysis patients have various cardiac disorders including ischemic heart disease, hypertensive cardiomyopathy, valvular heart disease, arrythmias, and pericarditis [7]. However, dialysis patients can also experience noncardiac edema, which occurs in about 25% of dialysis patients with congestion as a result of fluid overload rather than as a result of specific structural or functional abnormality of the heart [8]. The cause of congestion therefore must be carefully investigated on the basis of medical interview and physical findings. Previously referred to as high-output HF, noncardiac edema is most frequently caused by volume overload due to high salt intake, severe anemia, arteriovenous fistula with high blood flow, or hyperglycemia [9]. When investigating edema in hemodialysis patients, examinations should be performed before dialysis, when body fluid volume is at its highest [10]. The method used for the diagnosis of HF in hemodialysis patients is similar to that used for non-dialysis patients [11], though there are some limitations in the use of biomarkers, as discussed in the next section.

Cardiac biomarkers

Cardiac biomarkers have been utilized to predict CV morbidity and mortality in asymptomatic patients with CVD [12], but their application has been limited in patients on dialysis due to heterogeneity in the relationships between elevated biomarkers and outcomes. BNP and NT-proBNP are biomarkers released in response to ventricular stretch or ischemia [13]. Among

Table 1 Definition of heart failure

Definition of heart failure in the present guidelines	Clinical syndrome consisting of dyspnea, fatigue, edema, and/or decreased exercise capacity owing to the loss of compensation for cardiac pumping function caused by structural and/or functional abnormalities of the heart
Definition of heart failure for the public (patient-friendly version)	Heart failure is a heart disease that causes shortness of breath and swelling, gets worse with time, and shortens life expectancy

Table 2 Classification of heart failure by LVEF on examination

Phenotype	LVEF	Definition
Heart failure with reduced ejection fraction: HFrEF	< 40%	Left ventricular systolic dysfunction. In many clinical studies, patients with a low LVEF despite standard medical treatment for heart failure are enrolled as patients with HFrEF
Heart failure with preserved ejection fraction: HFpEF	≥ 50%	Left ventricular diastolic dysfunction. Other diseases that may cause similar symptoms should be ruled out. No effective treatments have been established
Heart failure with mid-range ejection fraction: HFmrEF	40% to < 50%	Borderline heart failure. Clinical features and prognosis have not yet been fully characterized. Treatment should be selected on an individual basis

LVEF left ventricular ejection fraction

asymptomatic euvolemic patients on dialysis, serum BNP and NT-proBNP levels are often more than 20 times the upper limit of normal range [14]. A systematic review and meta-analysis has found that baseline BNP and NT-Pro BNP levels are still significantly associated with CV morbidity and mortality in patients on dialysis [15]. Considering the heterogeneity in previous studies of these biomarkers, there is a need to establish a standard value for the diagnosis of HF in dialysis based on values measured at an appropriate dry weight in the absence of clinical symptoms of HF [14]. Obokata et al. reported that soluble isoforms of ST2 (sST2), galactin-3 (Gal-3), and NT-proBNP were associated with all-cause mortality in chronic hemodialysis patients [16]. Both sST2 and Gal-3 had independent and incremental prognostic values over NT-proBNP in these patients. Assessment of sST2 and Gal-3 further enhances risk stratification.

Diagnostic procedure

The standard concept for diagnosing HFpEF is based on the following three points: (i) presence of HF symptoms, (ii) normal or increase LVEF, (iii) signs of LV diastolic dysfunction [17]. Clinical guidelines in both Japan and western countries have set an LVEF of 50% or higher as the standard for diagnosing HFpEF [6, 11], which present in about half of patients with HF [18]. However, diastolic dysfunction is difficult to diagnose in routine practice and there is a lack of diagnostic criteria for HFpEF. Thus, the combined use of various echocardiographic indices has been proposed as a comprehensive diagnostic strategy [19, 20]. Considering the strong association between HFpEF and background factors such as advanced age, diabetes, obesity, hypertension, atrial fibrillation, and coronary artery disease [21], screening for HFpEF is also a useful strategy. The H2FPEF score is calculated on the basis of obesity, advanced age, hypertension requiring polypharmacy, atrial fibrillation, pulmonary hypertension, and left atrial pressure elevation and has been proposed as simple screening method [22].

HFpEF is also recognized during the course for other conditions such as tachycardia-induced cardiomyopathy, ischemic heart disease, and dilated cardiomyopathy, reflecting improvement of LVEF due to the effects of treatment (Table 3, Fig. 1). Such cases are classified as HF with recovered EF (HFrecEF). Previous clinical studies have found that about 20–40% of HFrEF or HFmrEF cases transitioned to HFrecEF [23–26]. Background factors associated with HFrecEF include young age, female sex, and nonischemic heart disease, and among patients with HFrEF at onset of HF, those who improve

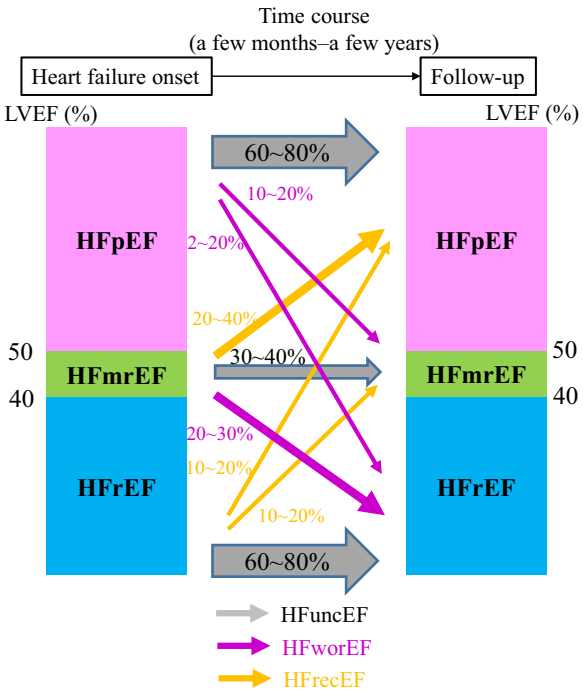

Fig. 1 Relationship between classification of heart failure by left ventricular ejection fraction (LVEF) onset and follow-up based on time-dependent changes in LVEF. Recreated from Fig. 1 in reference [5] under the Creative Commons BY-NC-ND license

Table 3 Classification of heart failure based on time-dependent changes in LVEF

Changes in phenotype	Definition
Heart failure with recovered EF: HFrecEF	LVEF improved during the treatment course and the condition transitioned from HFrEF to HFmrEF or HFpEF, or from HFmrEF to HFpEF The outcome is relatively favorable
Heart failure with worsened EF: HFworEF	LVEF decreased with the treatment course and the condition transitioned from HFpEF to HFmrEF or HFrEF, or from HFmrEF to HFrEF The outcome is poor
Heart failure with unchanged EF: HFuncEF	No major change is observed in LVEF throughout the course

HFmrEF heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LVEF* left ventricular ejection fraction

to HFrecEF have comparatively favorable outcomes [23, 24, 27].

Therapeutic management

The treatment of HF generally involves the management of comorbidities such as obesity, hypertension, and diabetes; nonpharmacological management such as lifestyle modification, management of symptoms, and disease-modifying therapy, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralcorticoid receptor antagonists (MRAs). Although broadly similar, the management of patients on dialysis is more complex. For example, volume management and medication adjustments are important considerations, and multidisciplinary care involving cardiologists, nephrologists, and other professionals is required.

Management of dialysis patients with HFpEF is based on factors that may contribute to diastolic dysfunction, such as overhydration, hypertension, and myocardial ischemia. Volume retention is a high risk factor for dialysis patients with HF [28], the first choice of treatment is to control body fluid volume by restricting salt intake (5 g/day), and limiting interdialysis body weight gain at less than 3% of the dry weight for an interdialysis interval of 1 day and less than 5% for 2 days [12]. In patients with overt congestion, the first step is to adjust the dry weight downward to ameliorate hypervolemia, anemia is treated, arteriovenous flow is optimized, and blood glucose level is corrected, as appropriate.

In addition, strict blood pressure control is very important and has beneficial effects on LVH in dialysis patients [29]. In the case of hemodialysis three times a week, blood pressure increases during the periods between the dialysis sessions, which is associated with an increase in body weight, especially in older patients with high dry weights. Increased peripheral resistance may be associated with activation of the sympathetic nervous system. Sodium and water retention are also associated with hypertension in these patients. Various clinical trials have shown that intensive hemodialysis reduces blood pressure and need for using antihypertensive agents and is effective for the management of HFpEF. Treatment of excessive preload reduction can lead to the underfilling of the LV, drop in cardiac output, and hypotension. For these reasons, a valid alternative is more frequent or longer hemodialysis.

Patients with chronic HF and LV systolic or diastolic function often develop LV remodeling, which compensates for reduced cardiac output [30]. However, this gives rise to a vicious cycle compensation by LV remodeling and leads to worsening of systolic and diastolic functions. Disrupting this cycle is critical for improving outcome. On strategy is use renin–angiotensin system (RAS) inhibitors or β-blockers to suppress sympathetic nervous system activation and RAS activation [30, 31], both which promote LV remodeling [32]. For nondialysis patients, it is recommended to treat HF with RAS inhibitors in order to reverse LV remodeling, despite this causing LV dysfunction [32]. However, there is little information available on the effectiveness of RAS inhibitors and of β-blockers in hemodialysis patients with HF.

In 2021, the Japanese Circulation Society and Japanese Heart Failure society released the revised version of clinical guidelines on the diagnosis and treatment of acute and chronic heart failure [6], which included a treatment algorithm for HF (Fig. 2). HF often has a chronic and progressive clinical course, where patients with overt HF often have repeated episodes of acute exacerbation of HF. This leads to progression from stage C (HF stage) to stage D (refractory HF stage). A strategy of cardiac rehabilitation is recommended for both of these stages, which involves multidisciplinary management and nonpharmaceutical management in the form of exercise therapy. In addition, palliative care is introduced early in stage C, with the aim of managing symptoms, improving quality of life, and supporting decision-making on treatment selection.

The therapeutic approach for stage C disease includes the treatment of acute exacerbations in both of chronic HF and acute HF. In the chronic phase of stage C, LVEF is the major concern, and the goal is to treat HFrEF with the maximum tolerable dose of ACE inhibitors or ARBs in combination with β-blockers, which have been reported to improve the clinical outcomes [6]. Combination therapy with an MRA plus an ACE inhibitors and ARB is the mainstay of treatment for HFrEF. In patients with symptomatic HFrEF, replacement for an ACE inhibitor or ARB with an angiotensin receptor–neprilysin inhibitor (ARNI) is recommended to improve morbidity and mortality. ARNIs can also be considered as an alternative to ACE inhibitors or ARBs in the initial treatment selection. Moreover, in patients with symptomatic HFrEF despite receiving optimal basic treatment, the addition of sodium–glucose co-transporter protein 2 (SGLT2) inhibitors is also recommended regardless of diabetes status in order to further lower the risk of HF exacerbation or CV mortality. Diuretics, on the other hand, have not been shown to improve survival, though they are necessary for symptom management and dose adjustment according to organ congestion is important. In patients with symptomatic HFrEF with sinus rhythm and 75 bpm heart rate or higher, addition of ivabradine is an option that should be considered in order to decrease the risk of hospitalization or CV death. If symptoms do not improve despite maximum and optimal pharmacologic therapy, the cardiac

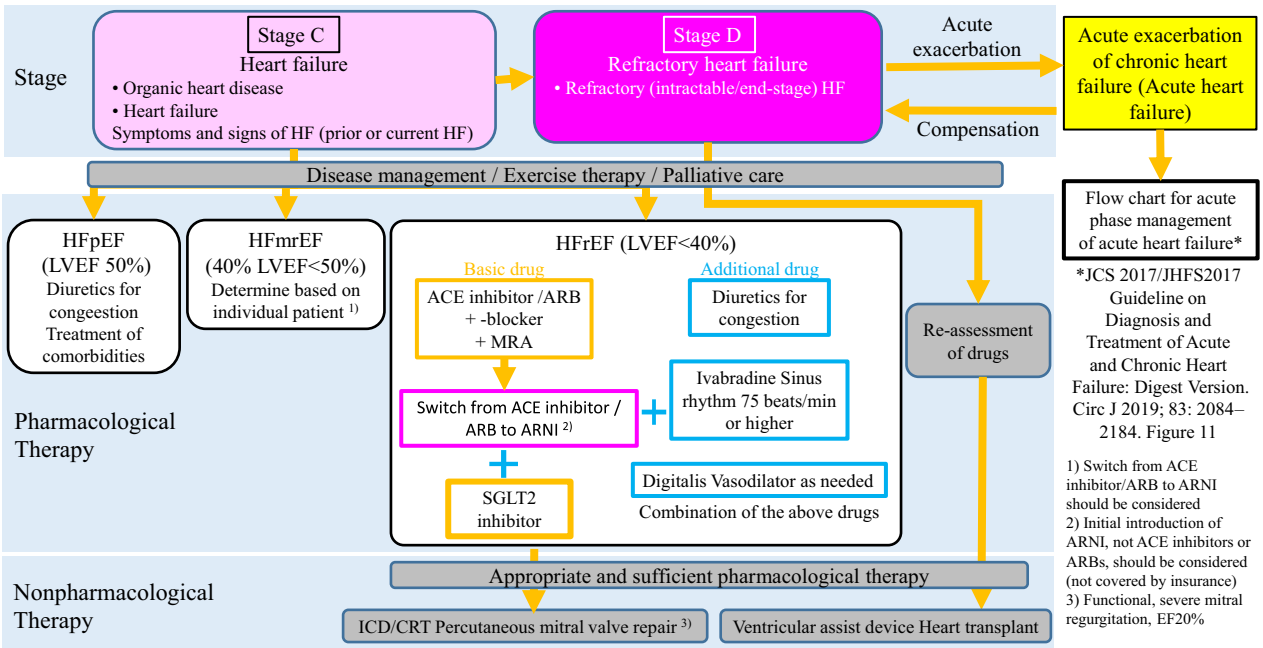

Fig. 2 Treatment algorithm for heart failure. Recreated from Fig. 1 in reference [5] under the Creative Commons BY-NC-ND license

resynchronization therapy is recommended. An implantable cardioverter defibrillator is indicated in cases requiring primary or secondary prevention of sudden death. Percutaneous mitral valve repair should be considered for symptomatic patients with HFrEF who have LVEF of at least 20% and severe mitral valve insufficiency despite optimal basic medical treatment. According to the treatment algorithm above, treatment for stage D disease is started when patients have severe symptoms even at rest, required repeated hospitalization.

A small portion of HFpEF patients exhibit the sympathetic and RAS system activation, and the prognostic significance of elevated plasma level of neurohormones in these patients has not been determined [33]. The safety and efficacy of ACE inhibitors for the treatment of HFpEF was investigated in three large-scale clinical trials [34–36]. The CHARM-Preserved and the I-PRESERVE trials investigated ARBs, and the PEP-CHF trial investigated an ACE inhibitor. CHARM-Preserved included patients with HFpEF (LVEF > 40%) who had a New York Heart Association (NYHA) class II–IV status and a history of hospital admission for HF, and its primary outcome—a composite of CV death and HF admission—was not met [hazard ratio (HR) 0.89; [95% confidence interval (CI) 0.77–1.03]; $p = 0.118$]. In an echocardiographic substudy of the CHARM-Preserved trial, only half of the enrolled patients had moderate or severe diastolic dysfunction, but it was a strong predictor of worse outcome [37]. In light of the results of the above trials, subsequent trials added echocardiographic evidence of diastolic dysfunction and congestion as additional inclusion criteria. The results were clearly similar in the more highly selected cohorts with ARBs having no impact on mortality and some effect on hospitalization for HF. A large meta-analysis of these clinical trials concluded that both ACE inhibitors and ARBs have no effect on all-cause mortality (HR 1.01; 95% CI [0.92–1.11]), CV death (HR 1.02; 95% CI [0.90–1.14]), and hospitalization for HF (HR 0.92; 95% CI [0.83–1.02]) [38].

The TOPCAT trial was a large, multicenter, randomized, double-blind, placebo-controlled clinical trial that examined the efficacy and safety of an MRA (spironolactone) in patients with HFpEF aged > 50 years who had at least one sign or symptom of HF, and LVEF > 45%, and prior hospitalization for HF within the past 12 months or an elevated BNP or NT-proBNP level [39]. Overall, there was no effect of the MRA on the primary outcome—composite CV death and hospitalization for HF (HR 0.89; 95% CI [0.77–1.04]; $p = 0.14$), and only hospitalization for HF was significantly reduced in patients treated with the MRA (HR 0.83; 95% CI [0.69–0.99]. $p = 0.04$). Two clearly diverging trajectories in the occurrence of the primary outcome emerged since the first publication of the results [40].

PARAGON-HF was a randomized controlled trial that compared a composite of total hospitalization for HF and CV death as the primary outcome in 4822 patients with NYHA class II–IV, EF > 45%, elevated BNP or

NT-proBNP, and structural heart disease between valsartan alone or sacubitril/varsartan, which is an ARNI [41]. The primary endpoint was not reached, with only a small number of events. When the outcome was split into its components, there was no effects on CV mortality (HR 0.95; 95% CI [0.79–1.16]) and a modest positive effect on hospitalization for HF (HR 0.85; 95% CI [0.72–1.00]). Addition of the ARNI also shows was also beneficial for some important secondary outcomes, including quality of life.

In contrast to RAS inhibitors, there is not a large body of evidence for the use of β-blockers in the treatment of HFpEF. Thus, β-blockers are primarily used to treat HFpEF based on the clinical judgement of the attending physician in tailored care. The population of patients with HFpEF is highly heterogeneous, with the underlying mechanisms and etiologies complicating the design of clinical trials of β-blockers for HF. The SENIORS trial enrolled patients with HF across the entire spectrum of LVEF values and randomized them to receive the β-blocker nebivolol or a placebo [42]. Among studies of β-blockers, the subgroup analysis of 752 patients with LVEF > 35% in the SENIORS trial is the largest cohort of patients with HFpEF in a placebo-controlled randomized study. The primary end point was reached in 235 patients of the patients with HFpEF (31.2%), and nebivolol was shown not to have a significant effect ($p = 0.720$). However, meta-analyses have suggested that β-blockers could reduce CV mortality or all-cause mortality without having a significant effect on hospitalization for HF [43, 44].

The efficacy and safety of new drugs such as SGLT2 inhibitors has been investigated in patients with HFpEF (EMPEROR-Preserved) [45] and those with HFmrEF (DELIVER) [46]. The addition of SGLT2 inhibitors has been shown to reduce CV death or worsening of HF, with relative risk reduction of 26% and 25%, respectively, when dapagliflozin and empagliflozin were trialed in patients with overt HF [46, 47]. The positive results of both of these trials demonstrated significant reductions in a composite of CV death and hospitalization for HF as the primary outcome. The magnitude of the effect was similar between EMPEROR-Preserved (HR 0.79; 95% CI [0.69–0.90]; $p < 0.001$) and DELIVER (HR 0.82; 95% CI [0.73–0.92]; $p < 0.001$). These positive results were mainly attributable to a decrease in hospitalization for HF and worsening HF events. In both trials, the effect on CV deaths approached, but did not reach, the level of significance (HR 0.91; 95% CI [0.76–1.09] in EMPELOR-Preserve; HR 0.88; 95% CI [0.74–1.05] in DELIVER). Taken together, these trials show that empagliflozin and dapagliflozin significantly reduced the incidence of CV events and worsening of HF in patients with HFpEF. All of the above trials excluded patients on hemodialysis. This may partly explain the lower prescription of these drugs in patients with reduced renal function. However, evidence from these trials suggests that patients with kidney dysfunction may benefit from treatment with these agents.

In conclusion, few treatments have been shown to be effective in hemodialysis patients with HFpEF, though they are a group at high risk of death. Adequately powered clinical trials are needed to examine the benefits and harms of conventional therapy for HFpEF in the context of hemodialysis patients with HFpEF. We hope for further research that contributes to improving the clinical outcomes of these patients.

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K.N. planned the review, searched the literature, and prepared the article. K.K. searched the literature and assisted in writing the article. All authors read and approved the final manuscript.

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