Original Article

The role of myocardial perfusion SPECT in short-term cardiac prognosis of end-stage renal disease

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ABSTRACT

Introduction: One of the most important causes of death in patients with end-stage renal disease (ESRD) and even after kidney transplantation is cardiovascular diseases. Thus, cardiac evaluation is of utmost importance in the management of these patients especially during preoperative work up before renal transplantation. The aim of present study is to evaluate the role of myocardial perfusion imaging (MPI) in short-term prognosis of cardiac events in patients with ESRD.

Methods: In this cohort study, patients with ESRD who were referred for MPI before kidney transplantation, during a two years' time interval (December 2015- 2017) were evaluated. Those patients aged ≥30 years were included. Patients with a history of previous transplantation, congenital heart diseases, low MPI quality and incomplete /questionable history or follow-up data were excluded. The patients were subsequently followed by reviewing their hospital records, outpatient interviews and if required telephone contacts. The occurrence of cardiac related death, myocardial infarction and/or revascularization procedure was considered positive for short-term cardiac events.

Results: A total of 179 patients (67% males with mean age of 52 years) were included in this study. The mean follow-up duration was 15.3±6.6 months (2 to 32 months) during which, one hundred patients received kidney transplantation. The coronary artery disease (CAD), diabetes mellitus (DM), dyslipidemia and abnormal MPI findings were more prevalent in patients with cardiac events. Whereas those who had undergone kidney transplantation, developed fewer cardiac events during the follow up period. However, in multivariate Cox proportional hazard analysis only abnormal MPI findings and positive history of CAD were independent predictors of cardiac events. The kidney transplantation was a significantly protective marker. Other cardiac risk factors and none of quantitative perfusion parameters of MPI showed a significant association with cardiac events in multivariate Cox proportional hazard models.

Conclusion: According to our study, abnormal MPI and previous CAD history were the best predictor of short-term cardiac events. The kidney transplantation can lead to a better short-term cardiovascular prognosis.

Key words: SPECT; Myocardial perfusion imaging; Renal disease; End-stage

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INTRODUCTION

End-stage renal disease (ESRD) is associated with high rate of morbidity and mortality. Despite the therapeutic advances and increased rate of kidney transplantation, prognosis is still poor with cardiovascular disease being the most important cause of death after kidney transplantation [1, 2].

The higher rate of cardiovascular diseases in ESRD patients can be attributed, in part, to higher prevalence of well-known risk factors for coronary artery disease (CAD) in these patients such as hypertension and diabetes mellitus (DM). In addition, factors like endothelial dysfunction, calcium and phosphorous imbalance, anemia and lipoprotein abnormality, which are associated with cardiovascular problems, are reported to be higher in ESRD patients [1, 3-5]. However, the benefits of cardiac evaluation in asymptomatic patients awaiting for transplantation are questionable [1]. Since clinical symptoms and cardiac risk factors cannot effectively stratify ESRD patients [6, 7], stress tests and imaging modalities are widely used. According to the American Heart Association (AHA)/American College of Cardiology foundation (ACCF) statement, the main goal of preoperative cardiac evaluation is to reduce cardiovascular morbidity and mortality [8]. However, utility of routine guideline recommendations for perioperative cardiovascular evaluation in ESRD is limited due to specific features in ESRD patients [8]. Because of lower accuracy of noninvasive stress testing, this committee stated that: "Noninvasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions based on the presence of multiple CAD risk factors regardless of functional status" [8] indicating lack of adequate relevant evidence.

Single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), dobutamine stress echocardiography and coronary angiography are the most commonly used methods; however, the choice of the best modality with higher prognostic and diagnostic accuracy and lower rate of complication is still a matter of debate. Although coronary angiography is a useful procedure in detection of intraluminal CAD, disadvantages such as high cost and invasive nature limit the use of angiography as a first line modality in preoperative cardiac evaluation [3, 4, 7]. In addition, other side effects such as contrast-induced nephropathy can be an additional problem in both coronary angiography and coronary computed tomography angiography (CTA) exacerbating the compromised renal status, leading to increased sessions of dialysis [3, 9]. Magnetic resonance imaging can also put the ESRD patients at risk of gadolinium induced nephrogenic systemic fibrosis [9]. On the other hand, exercise stress test is also limited in these patients due to lower functional capacity and more prevalence of hypertension and subsequent left ventricular hypertrophy, which can also affect the test results [7].

MPI with pharmacologic stress is considered a safe method of CAD risk evaluation in ESRD patients. However, reports of diagnostic and prognostic ability of MPI in renal failure vary widely in different studies. While some studies report, low sensitivity and specificity of MPI there are other studies with promising results regarding the prognostic accuracy of MPI for pre-transplant cardiac evaluation [6]. In addition, the method of MPI interpretation (quantitative vs qualitative) and definition of abnormal MPI is not similar in different studies. The aim of this study was to assess the value of visual interpretation and different quantitative perfusion parameters of SPECT MPI in prediction of cardiovascular events in ESRD patients and the impact of other risk factors on their prognosis.

METHODS

Study population

In this cohort study, known ESRD patients who were referred for SPECT MPI as part of pre-transplant cardiac workup during December 2015 to December 2017, were evaluated. Patients aged ≥30 years old who were on dialysis for over 6 months were included. Those patients with congenital heart disease, insufficient quality of MPI, incomplete /questionable history or follow-up data were excluded. Data regarding the history of known CAD (based on the previous angiography results, history of previous revascularization or myocardial infarction (MI)) as well as history of DM, dyslipidemia, hypertension, smoking and family history of CAD based on the patient's report were collected from hospital files. Positive history for each of these factors as well as age≥60 years was considered as cardiac risk factors. This study was approved by the local ethic committee, Shiraz University of Medical Sciences, Shiraz, Iran.

SPECT MPI protocol

All patients underwent a two-day MPI protocol with dipyridamole stress test on the first day and rest phase on the second day. In our center, when there was no contraindication, we used dipyridamole vasodilator pharmacologic test (0.56 mg/kg IV infusion over 4 minutes). Two minutes after completion of dipyridamole infusion, 555-925 MBq (15-25 mCi), [^{99m}Tc]Tc-MIBI was injected. The same dose of activity was used for the subsequent rest phase of the study. SPECT acquisition was performed 60-90 minutes after radiotracer injection in both phases with a dual-head gamma camera dedicated to cardiac imaging. A 180° arch, from the right anterior oblique view to the left posterior oblique view, thirty-two 30-

second projections was used. Then, raw projection data was reconstructed by 3-dimensional (3D) ordered subsets expectation maximization (OSEM) algorithm (subset:4, order:8) with post-filtering (Butterworth; cutoff: 0.5, order: 8). Quantitative and semi-quantitative data including summed stress score (SSS), summed rest score (SRS), summed difference score (SDS) and transient ischemic dilation (TID) ratio as well as total perfusion deficit (TPD) at stress (TPDs) and rest (TPDr) with their difference (dTPD) were derived by Quantitative Perfusion SPECT(QPS) software. Furthermore, for the portion of studies acquired in gated mode, the quantitatively measured left ventricular (LV) ejection fraction, LV end-diastolic volume (EDV), end-systolic volume (ESV), summed motion score (SMS) and summed thickening score (STS), were also extracted from Quantitative Gated SPECT (QGS) software.

SPECT MPI images were also interpreted by two nuclear medicine specialist who were blinded to the patients' follow-up results. Interpretation was based on two categories: normal perfusion and abnormal perfusion including both ischemic and infarcted myocardium. All images were reviewed on a monitor screen. In the case of discordant interpretations, a third specialist reported the scan. The two similar results were considered as the final result. For patients who had two or more MPI before renal transplantation, we only considered the closest MPI study to transplantation or the last MPI available.

Follow-up

All patients were followed-up via phone call with questions about the evidence of any cardiac events including cardiac related death, MI, unstable angina (UA) or revascularization. If the incidence of the event was reported by the patients or their relatives during the follow-up period, further documentation was required to confirm and categorize the event. For patients who experienced an event, further follow up information after the event such as transplantation, history of a second event or another MPI was not considered. Patients, who were inaccessible, unreliable or uncooperative, were excluded from the study. Data regarding the date of kidney transplantation were also gathered from hospital records.

Statistical analysis

For statistical analysis, SPSS software (SPSS Statistics for Windows, version 18.0) was used. Data are represented as mean± standard deviation for continuous quantitative variables and number (%) for frequencies. Normality of distribution was checked for quantitative data by –Kolmogorov-Smirnov test. For the comparison of the frequency of qualitative parameters including gender ratio, abnormal MPI report, positive history of CAD, DM, hypertension, dyslipidemia, smoking, family history of CAD as well as incident of cardiac events and transplantation chi square test was used and for comparison of the mean value of quantitative parameters including age, TID, EF, EDV and ESV, independent t-test and for comparison of SSS, SDS, SRS, TPDs, TPDr, dTPD, SMS, STS and number of cardiac risk factors, Mann-Whitney test was applied due to normality test results. These parameters compared between event/nonevent and also transplanted/non-transplant groups as shown in Tables 1 and 2. Log-Rank (Mantel test) was used for comparison of Kaplan –Meier curves. For generation of these curves as well as univariate and multivariate Cox proportional hazard analysis, Stata software (StataCorp. 2015. Stata Statistical Software: Release 14.2. College Station, TX: StataCorp LLC) was applied. P value<0.05 was considered to be statistically significant in all analysis.

Table 1: Baseline clinical and demographic data of patients and comparison between transplanted and non-transplant group.

	Non- transplant (n=79)	Transplanted (n=100)	Total (n=179)	P value
Age (years)	53±9	51±10	52±10	0.305
Male	43(54.4%)	77(77%)	120(67.0%)	**0.001**
Abnormal MPI report	20(25.3%)	13(13%)	33(18.4%)	**0.035**
History of CAD	24(30.3%)	19(19%)	43(24.0%)	0.083
Diabetes mellitus	48(60.7%)	47(47%)	95(53.0%)	0.067
Hypertension	66(83%)	85(85%)	151(84.3%)	0.790
Dyslipidemia	46(58.2%)	38(38%)	84(46.9%)	**0.007**
Smoking	7(8.8%)	19(19%)	26(14.5%)	0.056
Family history of CAD	24(30.3%)	19(19%)	43(24.0%)	0.077
Number of risk factors	3.0±1.7	2.5±1.4	2.7±1.6	**0.034**
Number of cardiac events	25(31.6%)	9(9%)	34(19%)	**<0.001**

CAD: Coronary artery disease, MPI: Myocardial perfusion imaging

Table 2. Comparison of clinical factors and imaging parameters between the patients with and without cardiac events.

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	Cardiac event (n=34)	No cardiac event (n=145)	P value
Age	54±9	52±10	0.242
Male	19(55.8%)	101(69.6%)	0.124
Abnormal MPI report	20(58.8%)	13(8.9%)	**<0.001**
History of CAD	21(61.7%)	22(15.1%)	**<0.001**
DM	23(67.6%)	72(49.6%)	0.058
Hypertension	31(91.1%)	120(82.7%)	0.224
Dyslipidemia	20(58.8%)	64(44.1%)	0.123
Smoking	3(8.8%)	23(15.8%)	0.294
Family history of CAD	8(23.5%)	35(24.1%)	0.940
Number of risk factors	3.4±1.6	2.5±1.5	**0.007**
Transplantation	9(26.4%)	91(62.7%)	**<0.001**
SSS	10.0±9.3	4.7±3.8	**<0.001**
SRS	4.4±7.0	2.6±3.0	**0.297**
SDS	3.9±3.4	2.2±2.4	**0.024**
TPDs	11.0±10.2	4.8±4.1	**<0.001**
TPDr	6.1±9.6	1.4±2.2	**0.001**
dTPD	4.9±3.4	3.4±2.8	**0.014**
TID	0.99±0.14	1.01±0.11	0.403
EF	54.6±12.1	56.8±8.8	0.307
EDV	127.3±45.5	127.4±45.5	0.706
ESV	60.8±34.0	58.1±31.5	0.997
SMS	10.2±12.2	4.4±6.5	**0.008**
STS	4.6±3.7	1.4±3.4	**0.001**

P value < 0.05 is significant. MPI: Myocardial perfusion imaging, CAD: Coronary artery disease, DM: Diabetes Mellitus, SSS: Summed stress score, SRS: Summed rest score, SDS: Summed difference score, TPDs: Stress total perfusion deficit, TPDr: Rest total perfusion deficit, dTPD: Delta total perfusion deficit, EF: Ejection fraction, EDV: End-diastolic volume, ESV: End-systolic volume, SMS: Summed motion score, STS: Summed thickening score.

RESULTS

191 patients with ESRD who referred to our nuclear medicine department for MPI as routine pre-transplant cardiac evaluation, between the years 2015 to 2017, were included in the study. After excluding 12 patients due to inadequate or low quality data, 179 patients (mean age 52± 10 years, 67% males) were included in this study. The mean follow up period was 15.3±6.6 months (2-32 months). Gated acquisition had not been performed for 59 patients, so, functional parameters were extracted and analyzed for only 120 patients. Due to the prolonged waiting list, only 100 patients received renal transplant after SPECT MPI. Table 1 summarizes the baseline characteristics of the population in this study based on receiving transplantation or not during the follow up and in total patients. Abnormal MPI report, dyslipidemia, cardiac risk factors and cardiac events, as composite endpoints of cardiac death, MI/UA or revascularization, were more prevalent among patients who had not received renal transplant and the percentage of male patients was higher in the transplanted group. In both groups, the most prevalent risk factor was hypertension (Table 1). During the follow up, percutaneous intervention (PCI) was performed for 20 patients, 4 patients underwent coronary artery bypass graft (CABG), 3 patients had MI/UA and 7 patients died due to cardiac cause. Thus, these 34 patients formed the cardiac event group. Eight patients who had normal coronary angiography result and 137 patients, who had no cardiac event during the follow up, were included in the group with no cardiac event. Comparison of cardiac risk factors, MPI report and quantitative perfusion and functional MPI parameters in patients who developed with cardiac events during the follow up and event-free patients is shown in Table 2. Univariate Cox proportional hazard analysis for evaluation of potential predictors of cardiac events revealed that positive history of CAD, DM and dyslipidemia as well as presence of 3 or more cardiac risk factors had a statistically significant positive association with cardiac events while renal transplantation had a significantly protective effect. Additionally, abnormal visual scan report, higher SSS, SDS, SRS, TPDs, TPDr, SMS and STS were also significantly associated with cardiac events (Table 3).

Table 3: Univariate Cox proportional hazard analysis for clinical factors and MPI parameters.

	HR	95% CI for HR Lower-upper	SE	P value
Age	1.02	0.99-1.06	0.01	0.150
sex	1.59	0.81-3.15	0.55	0.175
Abnormal MPI report	**8.32**	4.18-16.54	2.91	**<0.001**
History of CAD	**5.61**	2.81-11.22	1.98	**<0.001**
DM	**2.36**	1.15-4.88	0.87	**0.019**
Hypertension	2.48	0.75-8.13	1.50	0.134
Dyslipidemia	**2.10**	1.05-4.18	0.73	**0.034**
Smoking	0.53	0.16-1.74	0.32	0.299
Family history of CAD	1.66	0.73-3.76	0.69	0.219
Number of risk factors	**1.45**	1.17-1.80	0.16	**0.001**
Risk factors ≥3	**3.26**	1.51-7.03	1.27	**0.002**
Transplantation	**0.21**	0.09-0.46	0.08	**<0.001**
SSS	**1.09**	1.05-1.13	0.01	**<0.001**
SSS≥4	**3.16**	1.60-1.21	1.09	**0.001**
SSS≥8	**3.28**	1.53-7.06	1.28	**0.002**
SDS	**1.18**	1.06-1.31	0.06	**0.002**
SDS≥3	1.59	0.80-3.10	0.55	0.180
SRS	**1.08**	1.01-1.14	0.03	**0.009**
TPDs	**1.08**	1.04-1.11	0.01	**<0.001**
TPDs≥5	**3.02**	1.43-6.34	1.14	**0.003**
TPDr	**1.08**	1.04-1.11	0.01	**<0.001**
dTPD	**1.10**	0.99-1.20	0.04	0.060
TID	0.35	0.02-6.12	0.51	0.473
EF	0.98	0.94-1.02	0.01	0.492
EDV	1.00	0.99-1.00	0.00	0.841
ESV	1.00	0.99-1.01	0.00	0.811
SMS	**1.04**	1.00-1.08	0.01	**0.014**
STS	**1.07**	1.01-1.13	0.03	**0.010**

P value < 0.05 is significant. MPI: Myocardial perfusion imaging, HR: Hazard ratio, CI: Confidence interval, SE: Standard error, CAD: Coronary artery disease, DM: Diabetes Mellitus, SSS: Summed stress score, SDS: Summed difference score, SRS: Summed rest score; TPDs: Stress total perfusion deficit, TPDr: Rest total perfusion deficit, dTPD: Delta total perfusion deficit, EF: Ejection fraction, EDV: End-diastolic volume, ESV: End-systolic volume, SMS: Summed motion score, STS: Summed thickening score.

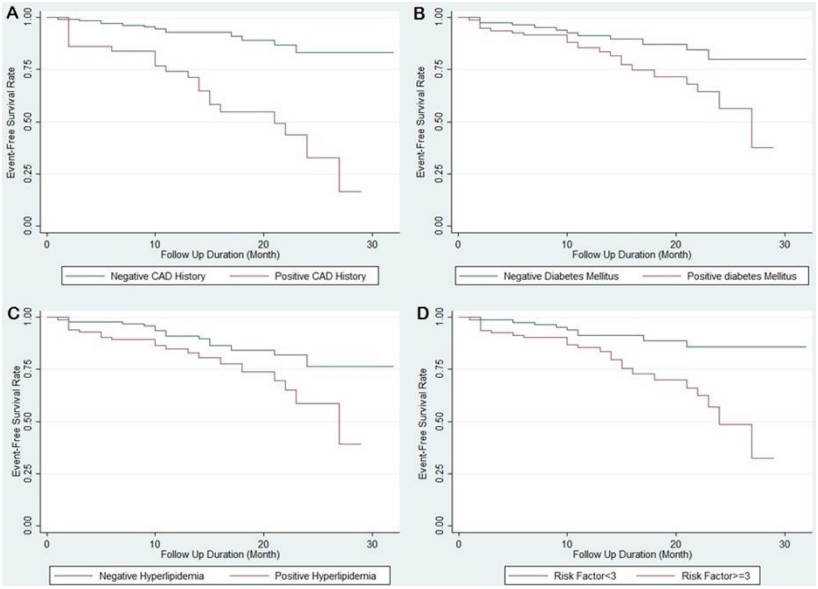

Fig 1. Kaplan-Meier event-free survival curves for comparison of event-free survival rate between the patients with positive or negative history of previous CAD (Log-Rank P<0.001) (A), DM (Log-Rank P: 0.015) (B), dyslipidemia (Log-Rank P: 0.029) (C) and between patients with ≥ 3 risk factors and those with <3 risk factors (Log-Rank P: 0.001).

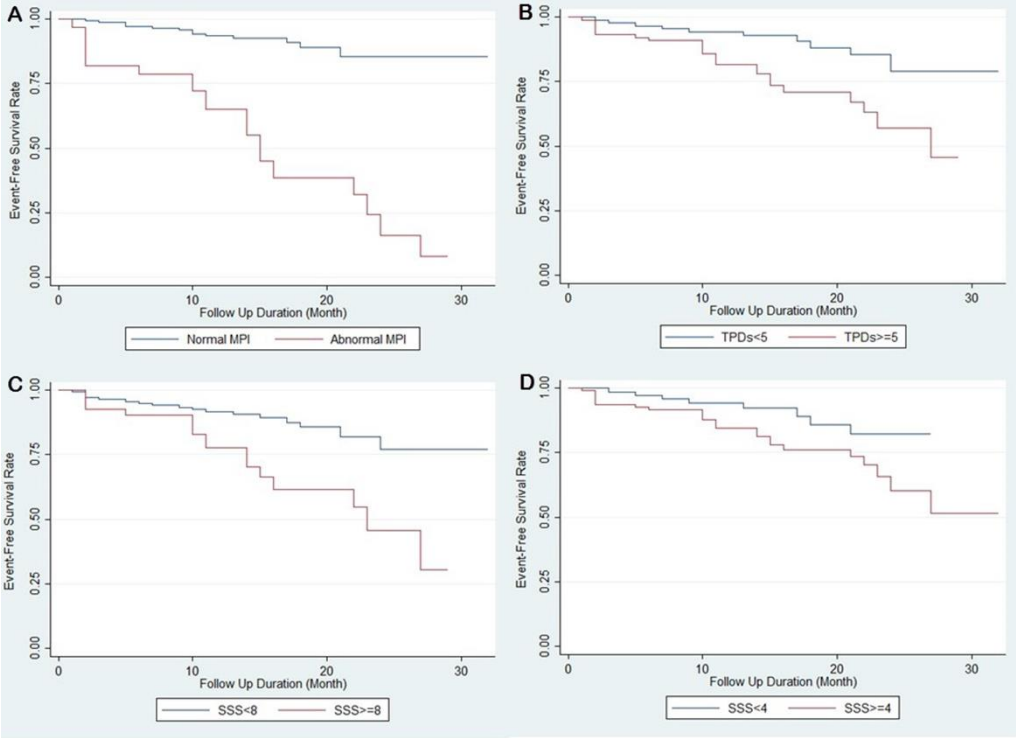

Fig 2. Kaplan-Meier event-free survival curves for comparison of event-free survival rate between the patients with abnormal and those with normal MPI report (Log-Rank P<0.001) (A), for those with TPDs≥5 and TPDs<5 (Log-Rank P: 0.002) (B), SSS≥8, SSS<8 (Log-Rank P<0.001) (C) and patients with SSS≥4 and SSS<4 (Log-Rank P: 0.030) (D).

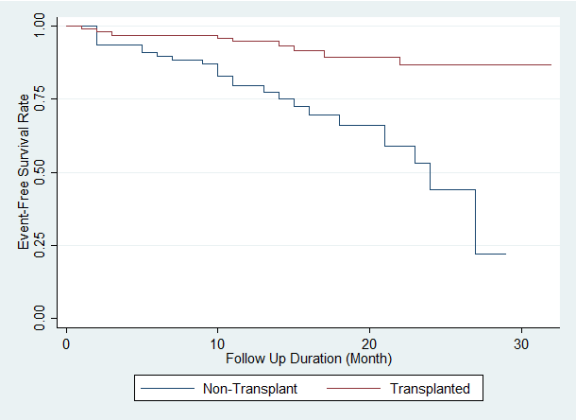

Fig 3. Kaplan-Meier event-free survival curves for comparison of event-free survival rate between the transplanted and non-transplant patients (Log-Rank P<0.001).

Figure 1 shows a significantly lower event-free survival rate for patients with previous history of CAD, DM, dyslipidemia and when 3 or more clinical risk factors are present. Figure 2 shows a significant difference between patients with normal and abnormal MPI reports, TPDs≥5 and TPDs<5, SSS≥8 and SSS<8 as well as those with SSS≥4 and SSS<4). Event-free survival rate was also significantly higher for patients who received kidney transplant during the follow up (Figure 3).

To evaluate the effect of confounding factors and to find the independent predictors of cardiac events, multivariate Cox proportional hazard model analysis was performed for variables, which had a p value of <0.05 in univariate Cox proportional analysis. Table 4 shows that only positive CAD history and abnormal MPI report were independent predictors of cardiac events and transplantation had a significantly preservative effect.

For better evaluation of perfusion parameters of MPI, we put each set of perfusion analysis, separately in multivariate Cox proportional hazard analysis (Table 5). Model 1 include only visual MPI report, model 2 includes semi quantitative parameters of SSS, SDS and SRS and model 3 consists of TPDs, TPDr and dTPD as MPI perfusion result. Among these methods of perfusion assessment, only abnormal MPI report based on visual evaluation is significantly associated with cardiac events (HR:8.17, 95% CI: 2.85-23.39, p value<0.001).

History of previous CAD is significantly related to cardiac events in all three models, but transplantation has independent protective effect only in model 2 and 3.

Table 4: Multivariate Cox proportional hazard analysis for significant clinical factors and MPI parameters.

	HR	95% CI for HR Lower-upper	SE	P value
CAD history	4.03	1.33-12.15	2.26	**0.013**
DM	1.87	0.42-8.34	1.42	0.409
Dyslipidemia	0.87	0.24-3.16	0.57	0.843
Risk factors≥3	0.54	0.13-2.17	0.38	0.389
Abnormal MPI report	3.96	1.13-13.89	2.53	**0.031**
Transplantation	0.34	0.12-0.93	0.17	**0.037**
SSS≥8	1.34	0.32-5.57	0.97	0.680
SDS	1.05	0.86-1.28	0.10	0.587
SRS	1.01	0.91-1.12	0.05	0.777
TPDs≥5	2.35	0.49-11.12	1.86	0.271
TPDr	1.00	0.91-1.10	0.04	0.881
SMS	0.92	0.81-1.03	0.05	0.170
STS	1.11	0.91-1.35	0.11	0.279

P value < 0.05 is significant, MPI: Myocardial perfusion imaging, HR: Hazard ratio, CI: Confidence interval, SE: Standard error, CAD: Coronary artery disease, DM: Diabetes Mellitus, SSS: Summed stress score, SDS: Summed difference score, SRS: Summed rest score, TPDs: Stress total perfusion deficit, TPDr: Rest total perfusion deficit, SMS: Summed motion score, STS: Summed thickening score.

Table 5: Three different multivariate Cox proportional hazard models for significant clinical factors and imaging data based on three different method of perfusion assessment by MPI

		HR	95% CI for HR Lower-upper	SE	P value
Model 1	**Abnormal MPI report**	8.17	2.85-23.39	4.38	**<0.001**
	CAD history	3.15	1.17-8.46	1.58	**0.023**
	DM	1.27	0.34-4.66	0.84	0.712
	Dyslipidemia	1.46	0.47-4.50	0.84	0.506
	Risk factors≥3	0.53	0.127-2.26	0.39	0.397
	Transplantation	0.41	0.16-1.05	0.19	0.064
	SMS	0.93	0.83-1.03	0.05	0.188
	STS	1.11	0.96-1.28	0.08	0.156
Model 2	**SSS≥8**	3.27	0.96-11.21	2.04	0.057
	SDS	1.11	0.94-1.31	0.09	0.191
	SRS	1.04	0.95-1.14	0.04	0.373
	CAD history	5.27	1.86-14.89	2.79	**0.002**
	DM	1.69	0.38-7.48	1.28	0.483
	Dyslipidemia	0.84	0.23-3.02	0.54	0.797
	Risk factors≥3	0.84	0.22-3.17	0.56	0.797
	Transplantation	0.29	0.11-0.80	0.15	**0.017**
	SMS	0.92	0.82-1.03	0.05	0.180
	STS	1.12	0.95-1.32	0.09	0.176
Model 3	**TPDs≥5**	3.57	0.77-16.41	2.78	0.102
	TPDr	1.04	0.96-1.12	0.03	0.249
	dTPD	1.06	0.89-1.25	0.09	0.496
	CAD history	3.79	1.41-10.19	1.91	**0.008**
	DM	1.86	0.48-7.18	1.28	0.363
	Dyslipidemia	0.67	0.19-2.37	0.43	0.543
	Risk factors≥3	0.83	0.20-3.36	0.59	0.796
	Transplantation	0.29	0.10-0.81	0.15	**0.018**
	SMS	0.96	0.86-1.07	0.05	0.522
	STS	1.02	0.86-1.20	0.08	0.777

P value < 0.05 is significant, MPI: Myocardial perfusion imaging, HR: Hazard ratio, CI: Confidence interval, SE: Standard error, CAD: Coronary artery disease, DM: Diabetes Mellitus, SMS: Summed motion score, STS: Summed thickening score, SSS: Summed stress score, SDS: Summed difference score, SRS: Summed rest score, TPDs: Stress total perfusion deficit, TPDr: Rest total perfusion deficit.

DISCUSSION

In this study, we demonstrated that in ESRD patients awaiting renal transplantation, abnormal MPI result as evidenced by any perfusion abnormality is associated with 8 times more cardiac events. Cardiac events were observed in 58.8% of patients with abnormal MPI while, there was no event in 91.3% of patients with normal myocardial scan (p value < 0.001). Although all quantitative perfusion parameters showed a significant difference between the patients with and without cardiac events, and based on univariate Cox proportional hazard models, only abnormal visual MPI report, previous history of CAD, and no kidney transplant, were the independent predictors of cardiac events.

Prognostic value of gated SPECT MPI in ESRD patients has been evaluated by different studies [10]. A systematic review by Wang et al. in 2012 revealed that abnormal test results in MPI defined, as reversible and/or fixed defects are associated with higher rates of major cardiac events and mortality. There are also a few studies with controversial results regarding the role of SPECT MPI in these patients. Jauhal et al. showed that abnormal MPI was not associated with greater risk of cardiac events or death during the mean follow up period of 5.4 years [11]. They categorized MPI as normal and abnormal scan based on the presence of reversible defects, wall motion abnormalities, lung uptake or TID. Winther et al. also evaluated 154 ESRD patients, before kidney transplantation. They concluded that the combination of CAD risk factors and CACS was the best approach for prognostication of ESRD patients and abnormal MPI, defined as SDS≥4, irreversible perfusion defects, EF≤45% or TID>1.22, could not predict major cardiac events or death [12]. On the other hand, in studies with favorable results towards the prognostic value of MPI, the main criteria for definition of abnormal scan are the presence of perfusion defects (reversible and/or fixed). In a study by Doukky et al. on 303 ESRD patients, abnormal MPI perfusion parameters and regadenoson-induced ischemia were associated with about 2-fold increase in composite end-point of cardiac death, MI, or coronary revascularization [13]. Helve et al. also revealed that even mild ischemia defined as <10% area of ischemic myocardium was associated with higher cardiac events [14]. Another study by Havel et al. showed that severe perfusion abnormality and CACS ≥ 1000 were significantly related to cardiac events in ESRD patients, however, functional parameters and TID ratio were not predictor of cardiac events [15]. Our study also showed that TID and other functional parameters are not associated with cardiac events. Although TID is considered as a potential prognostic marker in some studies, it is not fully evaluated in ESRD patients. On the other hand, measurement of TID and volume-derived functional parameters may be affected by left ventricular preload conditions associated with the inter-dialysis interval [16]. In summary, it can be stated that prognostic value of MPI for prediction of adverse cardiac events is mainly related to perfusion abnormalities whereas other generally reported ancillary findings of MPI such as TID, LHR and routine functional parameters need more investigation to be considered as the prognostic factors in patients suffering from ESRD.

Additionally, although some previous studies indicated comparable diagnostic ability of visual and quantitative parameters [17, 18], our results suggest higher prognostic ability of visual MPI report as compared to software-derived quantitative and semi-quantitative perfusion indices. This might be partly explained by specific characteristics of this group with expected higher LV volume, so higher rates of attenuation artifacts on the inferior wall, lead to miscalculation of perfusion scores by the software. Driessen et al. also showed the higher diagnostic accuracy of visual reading as compared to other non-attenuation corrected quantitative scores derived by software and similar accuracy with attenuation-corrected SSS and TPDs [19]. Nakajima et al. suggested higher prognostic performance for software-derived scoring when visual correction was applied to decreased scoring error due to attenuation of lower basal segment counts [20]. Thus, the prognostic value of visually assessed MPI alone or in combination with quantitative parameters appear to be superior to software-derived only scores, which is applied in most of the previously reported prognostic studies in these patients.

Our study also showed that the previous history of CAD is associated with higher cardiac events in pre-transplant candidates. Prognostic value of known risk factors of CAD in ESRD patients is questionable. According to AHA/ACCF recommendations, the presence of 3 risk factors are appropriate reasons to refer an asymptomatic patient for cardiac assessment [8]. However, our study showed that presence of 3 or more risk factors were not significantly associated with higher rates of cardiac events. Regarding this, there has been a notable difference in patient selection between our work and most of the previous studies. We included all the patients regardless of whether they received renal transplantation or not. The prevalence, distribution and prognostic ability of each cardiac risk factor as well as the duration of follow up are all important variables not similar among different studies.

Ives et al. also showed that MPI perfusion abnormalities presented as perfusion defect size, age>65years, history of DM, previous MI and blunted heart rate response to regadenoson were associated with higher rate of cardiovascular events [21]. In the

study by Helve et al., age, smoking and DM were also linked to worse cardiac prognosis in addition to myocardial ischemia [14]. Our study revealed that none of known cardiac risk factors, but previous history of CAD, was an independent predictor of cardiac events in the mean 15 months period of follow up. In addition, in a study by Nakamura et al., 529 patients with chronic kidney disease without known CAD, none of cardiac risk factors was associated with cardiac events [22]. On the other hand, our results indicated that transplantation had a significantly protective effect on the incidence of cardiac events. Only 9% of patients who had received kidney transplant developed cardiac events as compared to 31.6% of the patients who did not receive the transplant (HR;0.21, p value<0.001 by univariate Cox proportional hazard analysis). A previous study by Crosland et al. showed that transplantation could improve the cardiac function assessed by gated-SPECT MPI [23].

Study limitations

There were some limitations with our study. First, functional MPI parameters were not available for all patients, which may affect the reliability of these variables analysis. In addition, some previously reported prognostic factors such as the heart rate response to vasodilator stress and dyssynchrony indices could not be evaluated in our study. This was also a single-center study with relatively small sample size for a prognostic study. Larger cohort studies including other clinical and imaging parameters can better evaluate the results.

CONCLUSION

Considering the low prognostic ability of conventional cardiac risk factors in patients awaiting renal transplantation, inclusion of noninvasive cardiac tests with acceptable prognostic value such as SPECT MPI in the workup of ESRD patients would be a reasonable approach.

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