Prognostic Implication of Normalized Perfusion Scores in Patients with Known Coronary Artery Disease

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ABSTRACT

Background: Normalized perfusion scores allow uniform interpretation of both 17 and 20-segment models. This is a report on the additional prognostic implications of normalized perfusion scores beyond their conventional roles in clinical management.

Patients and methods: Patients undergoing gated SPECT myocardial perfusion imaging (GSMPI) with Adenosine stress from April 2018 to February 2019, were included in the study whose risk stratification and management recommendations were made using SS% and SD% respectively. The occurrence of cardiac events, quality of life (QOL), and management strategy were inquired about through a telephone interview in August 2020. An exploratory analysis was performed to find the significant interactions among imaging biomarkers, diabetes (DM), and the follow-up variables.

Results: Imaging data from 17 patients (seven having DM) with a mean age of 49.8 ± 10.4 were included. SS% was ≤14 in three patients and >14 in 14 patients. SD% was <10 in 12 patients and ≥ 10 in five patients. The SD% in DM patients suggested a similar extent of myocardial ischemia across the two SD% categories ($p > 0.05$). DM patients with a larger extent of ischemia had a greater stress-induced decline of LVEF ($p = 0.029$). SD% in DM patients with a stress-induced decline of LVEF was larger than those without a stress-induced decline of LVEF ($p = 0.048$). Follow-up data were available for 14 (82%) patients after a median interval of 26 months. Patients with non-improved QOL had larger perfusion defects in LCX territory, a higher proportion of cardiac soft events with SS% > 14, and CR despite an SD% < 10 ($p < 0.05$).

Conclusions: Normalized perfusion scores in addition to their interaction with DM and stress-induced decline of LVEF, may have prognostic implications in the prediction of post-GSMPI QOL.

Key words: Normalized perfusion score, Gated SPECT, myocardial perfusion imaging, QOL.

INTRODUCTION

The computer-generated semi-quantitative scoring of the extent and severity of left ventricular (LV) perfusion impairment, namely the summed stress score (SSS), summed rest score (SRS), and summed differential score (SDS) are derived from a five-point scale using a 17-segment polar map (1, 2). SSS predicts the risk for a cardiac hard event in patients with coronary artery disease (CAD) i.e. myocardial infarction or a cardiac death over the subsequent 12-months from a Gated SPECT Myocardial Perfusion Imaging (GSMPI). SDS predicts the likelihood of benefit from coronary revascularization (CR) over maximized medical management (MM). The 17-segment polar map is used by 4DMSPECT but the Cedars QPS, QGS, and the Emory Cardiac Toolbox use the 20 segments polar map (3). The risk strata for the 17-segment polar map model is inapplicable for scores derived from a 20-segment polar map. Normalized perfusion score surrogates for SSS, SRS, and SDS i.e., respectively, SS%, SR%, and SD% are calculated by dividing corresponding summed scores by a value corresponding to the segment numbers which are 68 for 17 segments or 80 for 20 segments, and then multiplying the result by 100 (2, 4). Thus the normalized perfusion score irrespective of its segment-model of origin can be interpreted using uniform interpretation criteria where the SS% is used to place the patient in one of the four risk strata (2) and the SD% is used to recommend either MM or CR (4-6). The predictive ability of SSS and normalized SS% has also been validated (7). The diagnostic utility (8, 9) and prognostic significance (10-12) of imaging biomarkers derived from GSMPI, particularly those of the perfusion scores (13, 14) is somewhat unique in patients with diabetes (DM). While the sensitivity of Adenosine stress GSMPI is reportedly satisfactory in Bangladeshi patients (15), the risk stratification and therapy recommendation was derived from a 17-segment polar map from 4DMSPECT for the past 20-years (16). This study was performed on a small series of patients labeled with normalized perfusion scores in order to explore the interaction of imaging biomarkers with DM, and patients' prognosis over a short term. Furthermore, the image data from a few representative cases were presented.

PATIENTS AND METHODS

Study population and imaging protocol

This cross-sectional study was conducted on a series of patients who had undergone GSMPI from April 2018 to February 2019 at the Institute of Nuclear Medicine and Allied Sciences (INMAS), Mitford. The pre-test diagnosis of CAD in these patients as well as their referral were done by cardiologists and cardiac surgeons. Briefly, the SPECT acquisition with ECG gating was done following standard acquisition protocol using a double detector SPECT-CT scanner (Siemens Truepoint). All patients underwent a one-day stress-rest protocol. Vasodilator stress with Adenosine was used and the radiotracer was essentially Tc-99m-Sestamibi. Post-reconstructed DICOM images were analyzed using Cedars QPS and QGS. The normalized perfusion scores were derived from a 20-segment polar map. Clinical record and image interpretation of all patients were the source of clinical data.

Procedure of follow-up

The contact number of each patient was called up in August of 2020 by a nuclear medicine physician to conduct a semi-structured interview over the telephone either directly with the patients or with a concerned family member. Information regarding post-imaging clinical management strategy on each patient within this duration, the incidence of cardiac soft or hard events, patient's compliance to the management plan, and improvement of patient's quality of life (QOL) during the post-GSMPI period in comparison to that during pre-GSMPI were enquired. The relevant categorical data from the follow-up interview were included as variables.

Categorization of variables and response

For the simplified comparison between GSMPI derived risk and short-term outcome, the SS% was categorized in a dichotomized manner with those being > 14 as significantly high risk (2) and those with SS% ≤14 as non-high risk. Then, the categorization of SD% was done as <10 in whom CR was not recommended and SD% ≥ 10 where CR was recommended (2). Data were further categorized as non-diabetic (NDM) and diabetic (DM), and then according to the stress-induced decline of LVEF among the diabetics. Finally, post-GSMPI events were categorized as hard and soft while post GSMPI management strategies were categorized as MM and CR.

Descriptions of variables and analytic method

Categorical data were presented as frequencies and percentages. Continuous data were presented as means and standard deviations (SD) and value ranges. Comparison of means was done by the independent sample t-test to explore the distribution of the age and all the imaging biomarkers of continuous charac across the binary categories of DM. To explore the interaction between DM and normalized perfusion scores, we checked the distribution of imaging biomarkers among subgroups of patients. The imaging biomarkers of continuous characteristics used in the analyses were: stress LVEF, rest LVEF, the difference of LVEF (rest LVEF subtracted from the stress LVEF), SR%, SD%, SS%, mixed, fixed, and reversible perfusion defects for total LV myocardium, and three coronary territories. The patients were sub-grouped according to normalized perfusion scores as well as their DM status or being non-diabetic (NDM). There were four subgroups of patients based on SD% and DM: DM with SD% ≥ 10, DM with SD% < 10, NDM with SD% ≥ 10, and NDM with SD% < 10. Similarly, there were four subgroups of patients based on SS% and DM: DM with SS% > 14, DM with SS% ≤ 14, NDM with SS% > 14, and NDM with SS% ≤ 14. A non-parametric Kruskal-Wallis test was done for pairwise comparison among the sub-groups and a Holm-corrected p-value was used.

Comparison of means was done by the independent sample t-test to explore the distribution of the age and all the imaging biomarkers of continuous characteristic across the binary categories of the qualitative follow-up variables. The follow-up variables were: management strategy, patient compliance, cardiac soft event, and improvement of QOL.

To explore the interaction of cardiac soft-event or management strategy with the post-GSMPI QOL, the distribution of QOL improvement was checked across the sub-groups done according to normalized perfusion scores combined with the status of the event or the strategy of management. When the patients were sub-grouped according to SS% combined with the status of their corresponding event, the groups were: event with SS% ≤ 14, event with SS% > 14, no event with SS% ≤ 14, and no event with SS% > 14. The patient subgroups according to SD% combined with their corresponding management strategy were: CR with SD% ≥ 10, CR with SD% < 10, MM with SD% ≥ 10, and MM with SD% < 10. A non-parametric Pearson's chi-square test for the comparison of distribution between and within the sub-groups. All the subgroup comparison was done using the 'ggstatsplot' (17) functions on R.

## RESULTS

Overall characteristics of the study patients

Total 17 patients (M/F=15/2) with a mean age of 49.8±10.4 (31-70) underwent GSMPI with Adenosine stress within the

study period. All were diagnosed cases of CAD involving single vessels in seven, double vessels in four, and triple vessels in six patients. Four patients had previous CR. Table 1 shows that the mean sizes for total fixed and reversible perfusion defects were 12.3±15.7 and 21.1±16.2. The mean of LV ejection fraction (EF) at stress and rest were 39.8±10.2 and 44.1±13.9. According to SS%, 14 patients (82%) were found to be at high risk with a mean SS% of 34.9±11.7 while according to SD%, five patients (29%) with mean SD% of 21.0±8.9 were found to be candidates with possible benefit from CR.

Table 1: Overall imaging characteristics of patients (n=17)

Trait		Mean ± SD	Range
Fixed perfusion defect size			
	Total (n = 14)	12.3±15.7	1-49
	% of LAD territory (n=13)	28.4 ± 27.4	4-80
	% of LCX territory (n=8)	19.8±11.7	10-25
	% of RCA territory (n=3)	9.3±6.5	3-16
Reversible perfusion defect size			
	Total (n = 17)	21.1±16.2	1-43
	% of LAD territory (n=13)	40.3 ± 25.5	4-77
	% of LCX territory (n=5)	39.0 ±24.1	7-72
	% of RCA territory (n=4)	32.8 ± 18.3	14-49
LVEF			
	Stress	39.8±10.3	26-60
	Rest	44.1±13.9	24-65
SS%			
	≤14 (n=3)	10±3.3	6.3-12.5
	>14 (n=14)	34.9±11.4	17.5-50
SD%			
	<10(n=12)	4.3±2.8	0-8.75
	≥ 10 (n=5)	21.0±8.9	15-36.3
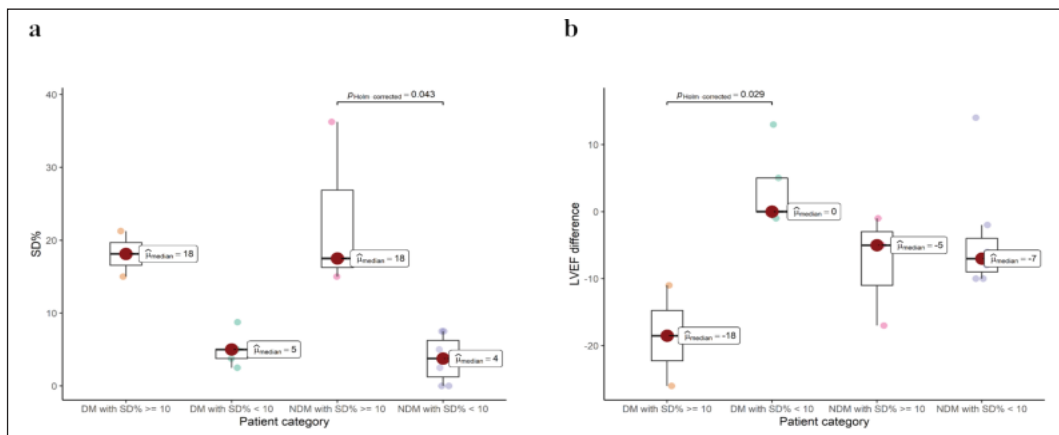
Figure 1: Distribution of imaging biomarkers among the patients sub-grouped based on SD% and DM. The distribution of SD% was significantly different among the two SD% categories of NDM patients (a), and the distribution of LVEF difference (rest LVEF subtracted from the stress LVEF) was significantly different among the two SD% categories of DM patients (b).

Interaction between DM and imaging biomarkers

A total of seven patients (41%, M/F=5/2) were diabetic in this series. The independent sample t-test failed to reveal any significant difference in the distribution of the age and all the imaging biomarkers of continuous characteristics across the binary categories of DM (data not shown). Among all the imaging biomarkers, only SD% and LVEF differences were found to be significantly different among the two of the subgroup pairs. All other non-significant distributions were not reported for simplicity while the significant paired comparisons are shown in Figure 1. The difference in the distribution of SD% reached significance among the NDM patient from the two SD% categories (Figure 1a). However, interestingly the paired comparison of DM patients shows a statistically similar SD% across the two different SD% categories. Figure 1b shows a significantly different distribution of LVEF difference among the DM patients from the two SD% categories. This indicates DM patients with a larger extent of ischemia had suffered from a greater stress-induced decline of LVEF (p = 0.029). Concordantly the SD% in DM patients with a stress-induced decline of LVEF (n=3) was significantly larger than those who did not have a stress-induced decline of LVEF (n=4) with the mean SD% being 13.8±8.2 and 5.0 ±2.7 (independent sample t-test, p-value 0.048).

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Characteristics of the patients available for follow-up

The median follow-up interval was 26 months (IQR 6 months) with the mean being 24.1±3.6 months.

Follow-up data (Table 2) were available for 14 (82%) patients; all were alive with no incidence of cardiac hard event.

Table 2: Major characteristics of the patients available for follow-up (n=14)

Characteristics	Frequency	SS%	SD%
Hospitalization due to angina	1	15	45
Quality of life			
Improved	8	34.2±14.1	12.3±12.6
Not improved	6	27.2±16.4	5.4±2.3
Management strategies			
Maximized Medical Management	9	31.8±15.1	10.4±12.1
Coronary Revascularization	5	30.2±16.4	7.5±4.9
Patient Compliance with management			
Compliant	11	29.7±16.1	9.7±10.8
Incompliant	3	37.1±9.7	8.3±8.0

Interaction of imaging biomarkers with the post-GSMPI QOL

The perfusion defect in LCX territory was significantly different across QOL categories with the means of mixed perfusion defect being 49.0±28.4 and 12.4±17.3 and the means of fixed perfusion defect being 23.8±13.3 and 10.0±0 between the non-improved and improved categories of QOL (independent sample t-test, p-values 0.023 and 0.038). No other distribution of imaging biomarkers across any other follow-up variables could reach a significant difference in distribution. No significant interaction of patient compliance with any other variable was found (data not shown).
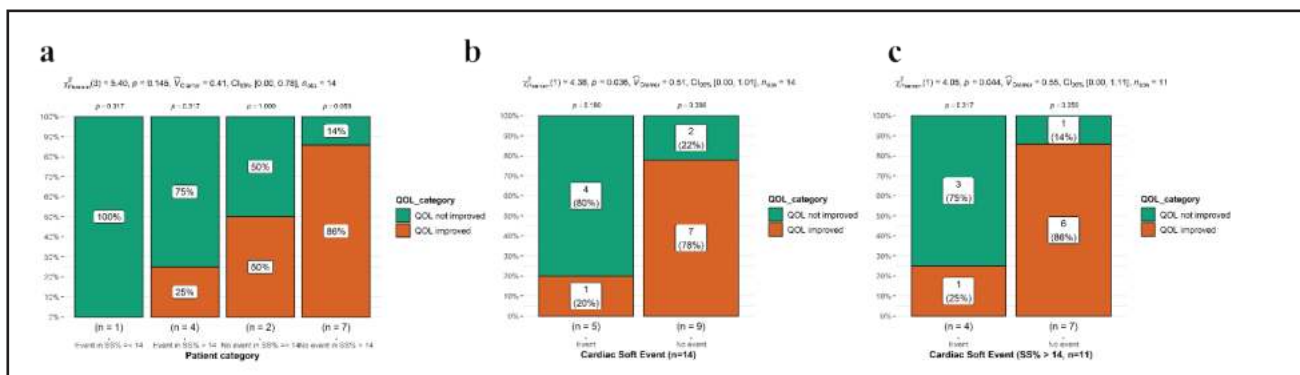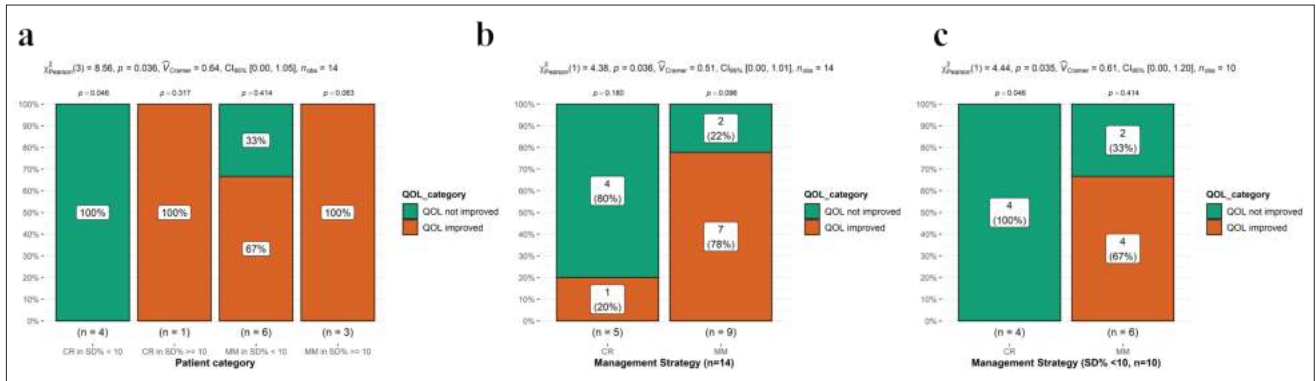

Figure 2: QOL among the patients sub-grouped according to SS% combined with the status of cardiac soft-event (a), with the overall association between cardiac soft-event and QOL improvement in 14 patients (b), and the association between cardiac soft-event and QOL improvement in patients who had SS% > 14 (c).

Interaction of cardiac soft-event with the post-GSMPI QOL

Figure 2a shows, that among the three patients with SS% ≤ 14, soft-event of CR occurred in one (33%). This patient had reported non-improved QOL during the follow-up interview. The other two patients reported having improved QOL with MM during their follow-up interviews. Among the patients with SS% > 14, a follow-up interview could be conducted with 11 patients. Four (36%) had a soft-event (CR in 3, hospitalization due angina plus CR in 1) with non-improvement of QOL in three. On the contrary, non-improvement of QOL was reported by one patient out

of the seven who experienced no cardiac event. Figure 2b shows that the proportion of QOL non-improvement in all the patients with cardiac soft-event was significantly higher than that in no event (Pearson chi-squared p-value 0.036). Figure 2c shows a similar trend in patients with SS% > 14 (Pearson chi-squared p-value 0.044). The distribution of QOL improvement within an event or non-event category was not significantly different for all patients as well as for those who had SS% > 14 (p > 0.05), although the proportion of QOL non-improvement tended to be higher in the event categories and lower in the no event categories.

Figure 3: QOL among the patients sub-grouped according to SD% combined with post-GSMPI management strategy (a), with the overall distribution of QOL improvement across the management strategies in 14 patients (b), and the distribution of QOL improvement across the management strategies in patients who had SD% < 10 (c).

*Interaction of management strategy with the post-GSMPI QOL*

Figure 3a shows, Among the four followed-up patients with SD% of ≥ 10, one (25%) had to undergo post-GSMPI CR while the other three were given MM. The QOL was claimed to be improved by all four patients, irrespective of management strategy. Among the 10 followed-up patients with SD% of <10, four (40%) had to undergo CR, resulting in no improvement of QOL in all of the four patients. On the contrary, non-improvement of QOL was reported in two of six patients with SD% of < 10, who were given MM. Figure 2b shows that the proportion of QOL non-improvement is significantly higher in all the patients with CR than those with MM (Pearson chi-squared p-value 0.036). Figure 2c shows similar trend in patients with SD% < 14 (Pearson chi-squared p-value 0.035). The distribution of QOL improvement within a CR or MM category was not significantly different for all patients as well as for those who had received MM with an SD% of < 10 (p > 0.05), although the proportion of QOL non-improvement tended to be lower in the MM categories. All patients who had CR despite SD% < 10 had reported non-improvement of QOL (Pearson chi-squared p-value 0.046).

Image sets from representative cases
The following images are five cases among the study patients, representative of various degrees of ischemia along with a description of their clinical management strategy and short-term QOL.
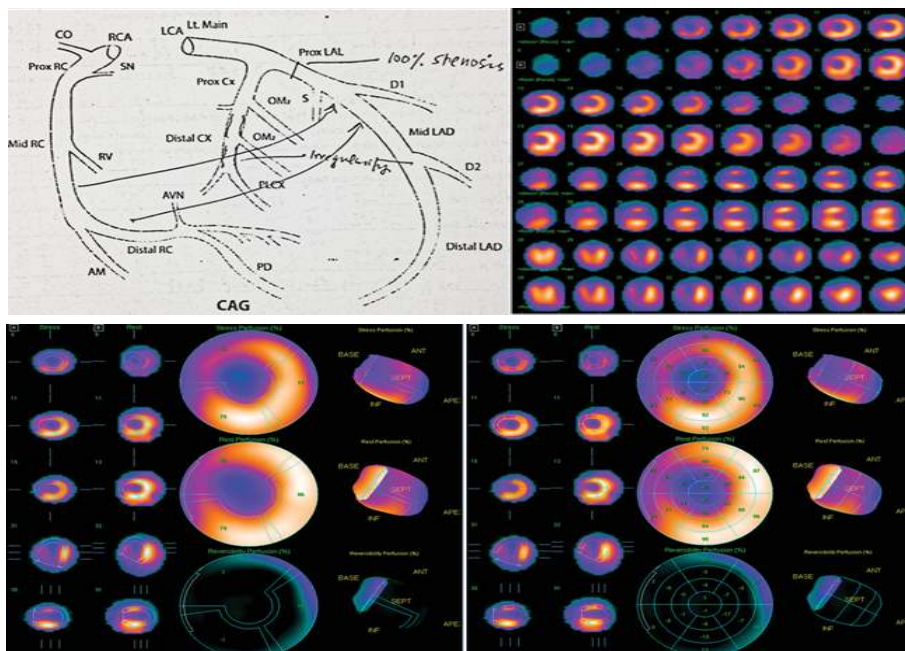
Figure 4: A 50 years old diabetic male, s/p medical management for extensive anterior MI with CAG proven total occlusion of proximal LAD. SPECT MPI after adenosine stress shows perfusion defect involving apex and all apical segments. No reversibility at rest– represents fixed perfusion defect (infarction) involving 77% myocardium in LAD territory (40% of total myocardium) SS% 40 (severely abnormal perfusion); SD% is 0 (no ischemia). QGS: LV was not dilated; LVEF at stress is 35% and rest is 45%. Apex and apical anteroseptal walls are hypokinetic at rest and nearly akinetic at stress. PTCA resulted in no improvement of QOL despite the patient's compliance.
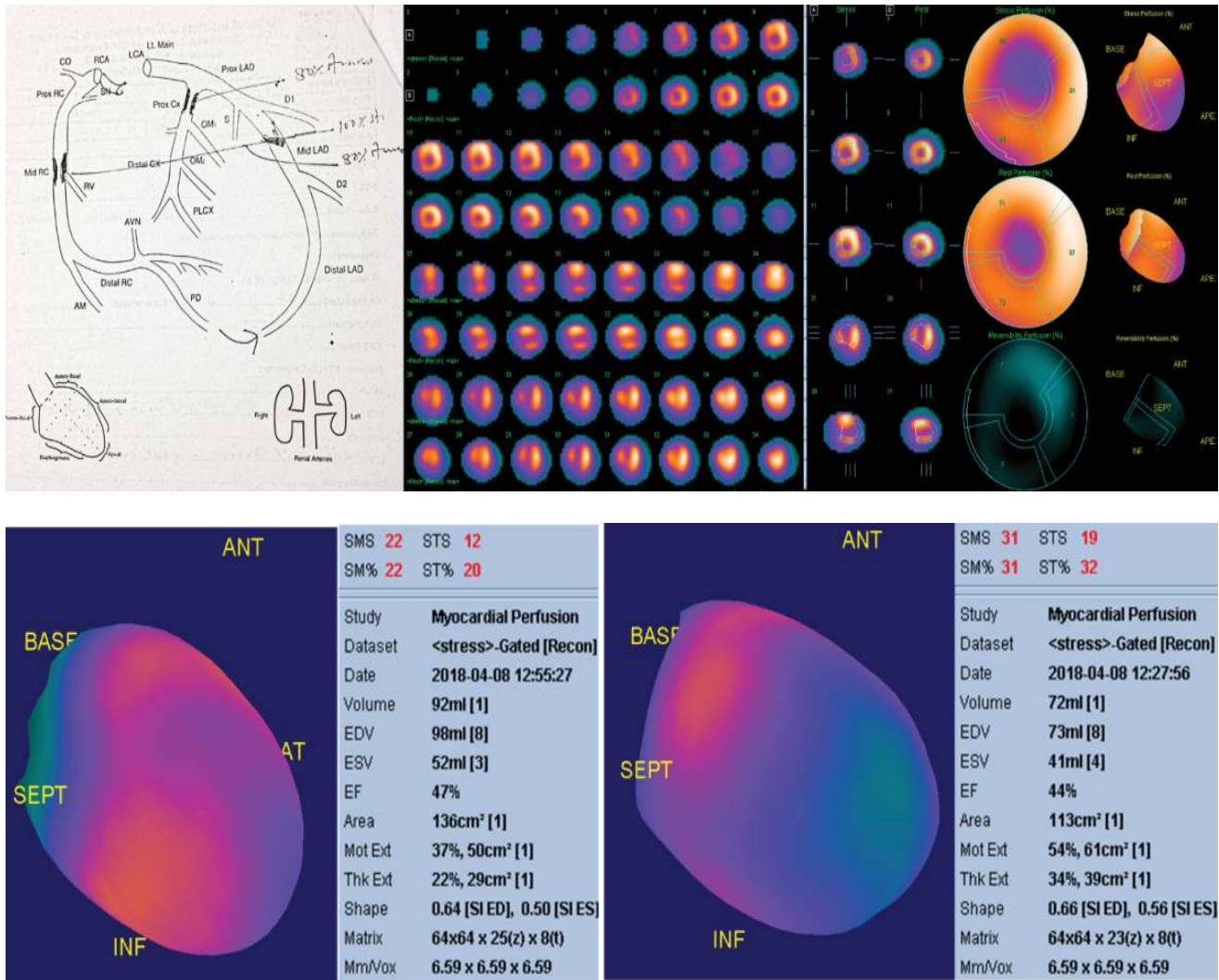
Figure 5: A 58 years old diabetic male, suffered from extensive anterior MI with CAG proven TVD. Adenosine stress GSMPI prior to CABG showed perfusion defect in apex, apical anterolateral, apical anterior & apical anteroseptal, mid anterolateral, mid anterior & mid anteroseptal. The area involved is about 59% in LAD and 25% in LCX territories, which is about 40% of the total LV myocardium. Rest images show reversibility in the mid-segment involved at stress which is about 2% of total LV myocardium. SS% is 40 (severely abnormal perfusion) and SD% is 2.5 (mild ischemia). QGS: LV is not dilated. The anterior wall is hypokinetic at rest which improves at stress. LVEF Stress 44% Rest 39%. CABG resulted in no improvement of QOL; however, the patient was non-compliant.

DISCUSSION

Findings in this small series suggest that DM patients despite having lower SD% can have a statistically similar extent of LV ischemia with that of higher SD% in both DM and NDM patients with known CAD. Therefore, these three groups may be considered for a similar course of clinical management. The prevention of ischemic events in DM patients with established CAD is highlighted as a key management priority by the influential guidelines (18) because the DM can lead to LV remodeling (9), a poor prognosis of CAD (19, 20), a rise of yearly cardiac event rate proportionate with the rise of SSS and SDS (14), and a doubled yearly cardiac event rate despite a normal GSMPI (13).

In the current series, 43% of DM patients had a stress-induced decline of LVEF which is known as an imaging marker of stunning (21, 22) with possible
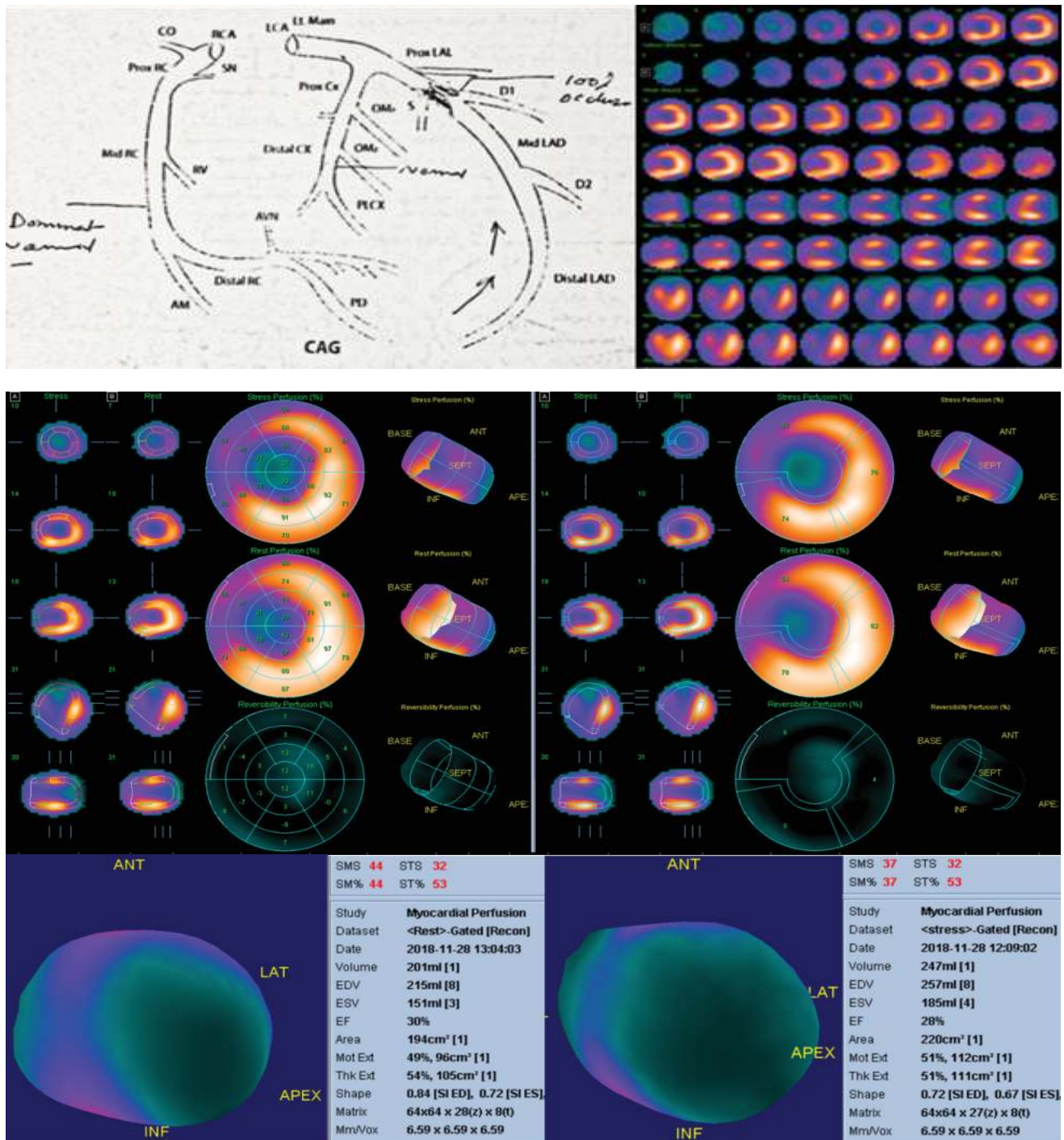
Figure 6: A 38 years old non-diabetic male, s/p treatment for NSTEMI with old anterior MI and having a CAG proven total occlusion of proximal LAD with retrograde filling, Adenosine stress SPECT MPI shows perfusion defect at stress involving apex, apical all segment, mid anteroseptal, and mid inferoseptal with mild reversibility in the segments with perfusion defect at rest except in apex, apical anterior, anteroseptal, inferoseptal and inferior – representing infarction (65%) with peri-infarct ischemia (12%) in LAD territory; 43 and 1% of total LV myocardium. SS% is 41.3 (severely abnormal perfusion) and SD% is 7.5 (moderate ischemia). QGS: LV cavity is markedly dilated, (EDV at stress 257 ml and at rest 215 ml; TID score 1.2). The anteroseptal wall is nearly akinetic both at rest and stress. LVEF at stress 28% and at rest 30%. Follow-up data was not available.
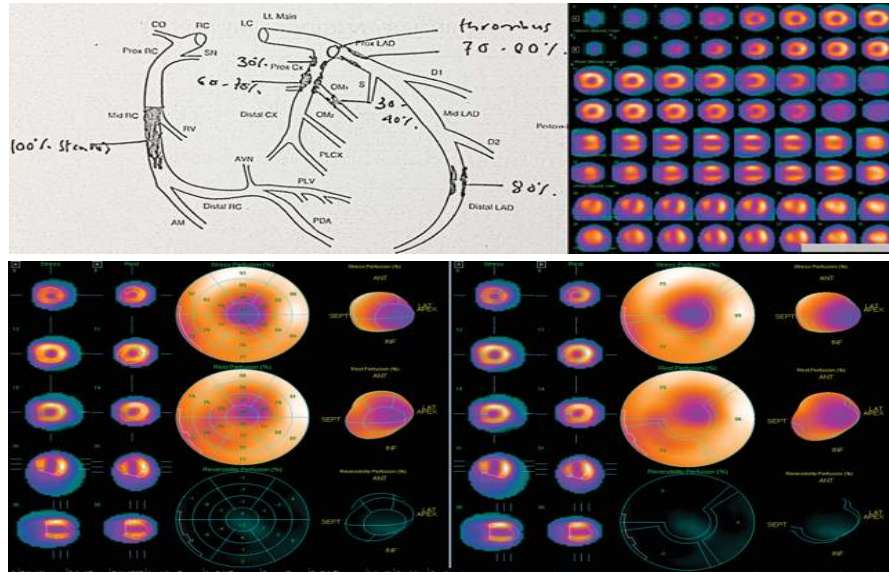
Figure 7: A 55 years old non-diabetic male, s/p treatment with LMWH due to STEMI (anterior) with CAG proven TVD. Adenosine stress GSMPI prior to CABG showed perfusion defect at stress involving apex and apical all segments with mild reversibility rest – representing fixed perfusion defect (infarction) involving 40% of myocardium in LAD territory (about 20% of total). SS% is 20 (severely abnormal perfusion) and SD% is 10 (borderline severe ischemia). QGS: LV cavity is not dilated. Apex and apical anteroseptal walls are akinetic at rest which became dyskinetic at stress. LVEF Stress 38%   Rest 24%. PTCA resulted in no improvement in QOL despite the patient's compliance.
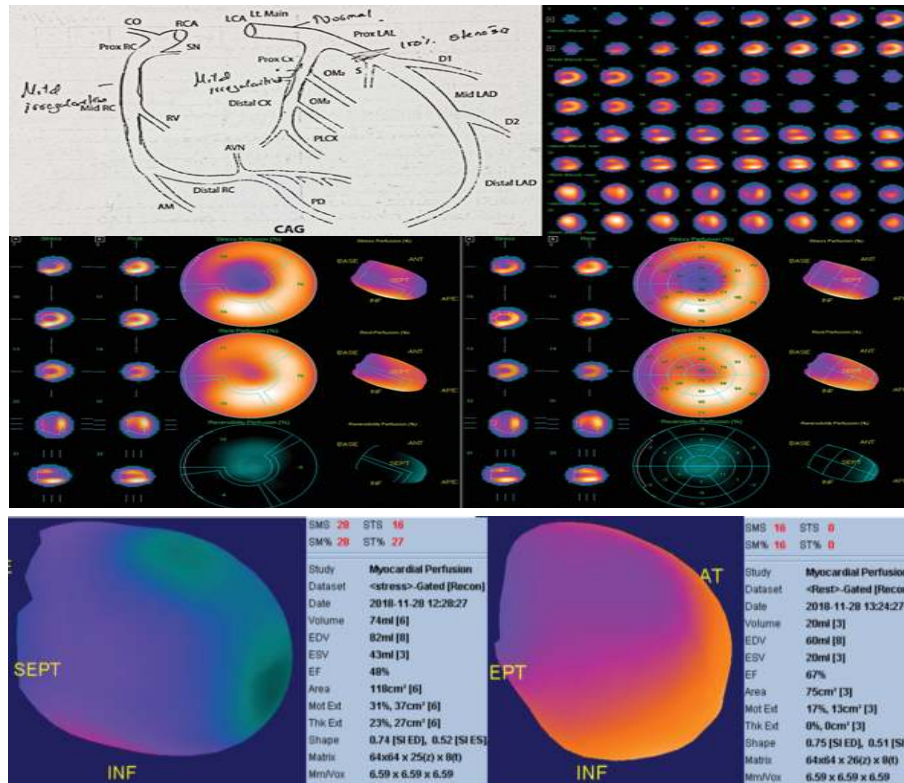

Figure 8: A 45 years old non-diabetic male, s/p treatment for NSTEMI with CAG proven total occlusion of proximal LAD. Adenosine stress SPECT MPI: perfusion defect involving apex, apical anterior-septal, apical anterior, and apical anterolateral segments with marked reversibility in all segments at rest except in apex – representing infarction (46%) with peri-infarct ischemia (26%) in LAD territory; 17 and 14% of total LV myocardium. SS% is 26.3 (severely abnormal perfusion); SD% 17.5 (severe ischemia). QGS: LV cavity not dilated. LVEF at stress is 48% and at rest is 67%. The apical anteroseptal wall is hypokinetic at stress which improves at rest. Compliance to MM resulted in improved QOL.

Prognostic implication of normalized perfusion scores

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prognostic significance (23). The higher SD% in those DM patients with a stress-induced decline of LVEF was concordant with stress-induced ischemia being a predictor of such decline (8). The finding of LCX territory having larger perfusion defects in the patients with non-improved QOL in series can be compared with the reports of worse clinical outcomes in LCX related myocardial infarction (24, 25)

The negative association between QOL and the post-GSMPI soft event, particularly in patients with SS% > 14 indicates even a soft cardiac event can render a patient to be less likely to experience an improved QOL over the short term. The negative association between QOL and management strategy in patients with SD% < 10 indicates that a CR despite low reversibility can render a patient to be less likely to experience an improved QOL over the short term. Taken together, the SS% and SD% may have an extended prognostic implication beyond their long-known utilities for the prediction of cardiac events and guidance of CR. A recent study has also found a positive association between cardiac positron emission tomography biomarkers and quantitative QOL indices (26).

There are several limitations of this study. The sample size was small. No data regarding the clinical rationale for the post-GSMPI management strategy was available, particularly in those cases of CR despite an SD% < 10. The assessment of QOL was qualitative and therefore subjective.

CONCLUSION

This series suggests an interaction of the normalized perfusion scores with diabetes and stress-induced decline of LVEF. The scores in addition to aiding the post-GSMPI clinical management may predict the QOL in patients during the short-term, especially those with high-risk SS% and those undergoing CR despite a low SD%.

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