INTRODUCTION

Chronic limb-threatening ischemia (CLTI) represents the end-stage of peripheral arterial disease (PAD), a problem of growing prevalence and increased health care costs around the globe [1]. CLTI is a highly morbid disease, incurring significant mortality, limb loss, pain, and diminished quality of life among those afflicted. Multiple health care specialists are involved in the management of CLTI, yet public awareness and early recognition continue to be major obstacles to effective treatment. Variability in practice patterns is also high, contributing to a broad disparity in the utilization of treatments and clinical outcomes. For example, recent studies in the United States suggest that many patients do not receive an angiogram in the year prior to major limb amputation. The studies also demonstrate a broad variation in the use of open or endovascular interventions by region of the country and hospital referral center [2]. More expensive (and more invasive) care is not associated with better outcomes [3]. Instead, what is lacking is a uniform definition of clinical stages of disease and key patient-focused outcomes, contributing to an incomplete picture of the epidemiology of CLTI and a limited evidence base to guide practice.

At the same time, rapidly evolving technologies in diagnostics, devices, drugs, and biologics, offer new opportunities to improve treatment and address unmet needs in this vulnerable population. A new framework is urgently needed in order to establish evidence based medical practice in this changing field. The rationale for a global guideline on the management of CLTI is based on this nexus of factors and the recognition of its growing impact on public health across all nations and socio-economic strata. Vascular specialists play a dominant role in the treatment of CLTI. In 2016 at ESVS (European Society of Vascular Surgery) conference the Global Vascular Guidelines (GVG) for CLTI were published [4]. The primary goal of this CLTI guideline is to improve the quality of care for all patients with CLTI, as well as for those at risk for CLTI.

Combining the Global Vascular Anatomical lower limb Classification (GLASS) with the clinically designed WIfI (Wound Ischemia and foot Infection) not only gives the idea of patient disease but also guide for the treatment.

REVIEW OF LITERATURE

The manifestations of chronic lower extremity ischemia often include pain produced by varying degrees of ischemia, ranging from no or atypical leg symptoms to typical exertional muscular pain (intermittent claudication) to ischemic rest pain. Patients may have more than one cause for their extremity pain, making diagnosis and management more difficult. Severe leg ischemia, characterized by rest/night pain and tissue loss (ulceration, gangrene), leads to significant morbidity and mortality and to the consumption of considerable health and social care resources in developed and developing countries. CLI is the most severe form of peripheral arterial disease and represents approximately 1% of total number of patients with PAD [5]. Chronic critical limb ischemia (CLI), defined as more than 2 weeks of rest pain, ulcers, or tissue loss attributed to arterial occlusive disease, is associated with great loss of both limb and life [6]. The management of lower extremity peripheral arterial disease is one of the most challenging problems of the vascular specialist. Decisions regarding the management of lower extremity PAD pose a unique challenge because of the complex interplay of factors that must be considered, including the underlying pathology, anatomic defects, degree of ischemia, availability of conduits, co-morbid conditions, functional status, ambulation potential, and suitability of anatomy for successful revascularization.

Appropriate management of lower extremity PAD requires a firm understanding of these factors for good decision making.

Several classification systems have been developed that characterize PAD on the basis of anatomic descriptions of lesion type and location. The major goals included standardization of reporting disease burden, development of methods to correlate disease burden with clinical severity, and development of recommendations for method of intervention. For Example

Bollinger Classification[7]

The Bollinger score, which was used by the BASIL (Bypass Vs Angioplasty In Severe Limb Ischemia) trial, utilizes a scoring system to classify angiographic lesions in terms of pattern and severity. The primary goal of this scoring system is to provide a semi quantitative method of evaluating atherosclerotic burden to facilitate comparisons either between patients or between time points (e.g. post interventions) for the same patient.

Graziani Classification [8]

The Graziani scoring system proposed a new morphologic categorization for disease severity among diabetic patients with CLI.

Trans Atlantic Inter Society Consensus Classification [9, 10] (TASC).

An updated document (TASC II) was published in January 2007 [10]. These important works went a step beyond the Bollinger and Graziani scoring systems, by not only classifying the lesions, but also by providing treatment recommendations according to lesion type. Recognizing the importance of the pathologic anatomy for decision making, the TASC working group has classified anatomic patterns of disease involvement (types A through D) for both the aortoiliac and femeropopliteal segments, based on recommended treatment (endovascular versus open surgery). Although the TASC guidelines are helpful, a grading system that is based on arterial anatomy alone is inadequate to guide therapy. Also there are two major problems with current classification systems:

(1) The validity and natural history of the concept of CLI, and

(2) The failure of most existing systems to assess and grade the major factors that influence both risk of limb loss and clinical management [11].

In modern practice, patients with a threatened lower extremity present with a broad spectrum of underlying contributory factors of which ischemia is just one component, albeit an important one, in determining whether that limb can be salvaged. Existing CLI classification systems fail to adequately categorize the extent of tissue loss or the presence and severity of infection. The clinical classification systems that include the broad categories of rest pain, ischemic ulceration, and gangrene (Rutherford 4, 5, and 6 [12] ; Fontaine III, IV [13]), while adequate for identifying patients at increased risk for major limb amputation and death, are not sufficiently detailed to stratify the range of risk or determine best therapy across this heterogeneous spectrum of patients. Controversies over revascularization approaches (open bypass vs. endovascular therapy) [14-16], and non-revascularization approaches (local wound care vs. hyperbaric oxygen therapy vs. cell-based therapy) [17-21] cannot be resolved without more precise stratification of the patients being treated. In addition, recent trends have focused excessively on anatomic extent of disease and arteriographic findings without sufficient emphasis on the physiologic state of the limb. An adequate classification system that risk stratifies patients and aids in clinical decision-making represents an enormous unmet need in the field of chronic limb ischemia (CLI). While limb perfusion and arterial anatomy are key factors in predicting amputation risk, so too are wound depth and presence and extent of infection.

Classification systems published to date have been of limited utility in clinical decision-making because of their overly narrow focus on specific aspects of the lower extremity at risk for amputation. TASC I, TASC II, the Bollinger system, and the Graziani morphologic categorization, for example, address only arterial anatomy, but fail to quantify the index wound or baseline perfusion status. An improved understanding of the underlying disease and advances in therapy, particularly endovascular procedures, has rendered existing classification schemes obsolete while simultaneously highlighting the need for a more comprehensive system.

GLASS classification [5] (Global Limb Based Anatomical Staging System)

GLASS classification is the new limb based classification which incorporates two novel and important concepts, the Target Arterial Path (TAP) and estimated limb-Based Patency (LBP). Based on appropriate angiographic imaging, the TAP is defined by the treating surgeon/interventionalist as the optimal arterial path to restore in-line flow to the ankle and foot, and resolve the clinical problem at hand. It may incorporate then either least diseased path or an angiosome-preferred strategy chosen by the clinician. The LBP is defined as maintenance of in-line flow throughout the entire length of the TAP, from groin to ankle. The complexity of disease traversed by the TAP from groin to ankle is integrated into the GLASS system. Femoropopliteal (FP) and tibiopreoneal (TP) arterial segments are individually graded on a scale from 0-4, and the grades are then combined into three GLASS stages for the limb, using a consensus-based patency. Using a consensus process, combinations of grade scores for the FP and TP segments were used to define **three GLASS stages** based on estimating the likelihood of immediate technical success [22] and 12-month LBP following endovascular intervention of the selected TAP. GLASS stages for the limb thus reflect a gradient of TAP complexity:

- **Stage I**: **Average Complexity Disease:** expected technical failure < 10% **AND** >70% 12-month LBP

- **Stage II**: **Intermediate Complexity Disease:** expected technical failure < 20% **AND** 12-month LBP 50-70%
- **Stage III**: **High Complexity Disease**: expected technical failure >20%; **OR** <50% 12-month LBP.

TABLE 1. GLASS: Key definitions and assumptions

• **Restoration of in-line flow** to the ankle and foot is a primary goal • **Target Artery Path (TAP):** the selected continuous route of in-line flow from groin to ankle. • The TAP usually involves the least diseased IP artery, but may be angiosome-based • **Limb-Based Patency (LBP)**: maintained patency of the TAP • Inflow disease (Aorto-Iliac and CFA) is considered separately, and assumed corrected • **Grade** within segment is determined by presence of any one of the defined descriptors within that grade (i.e. the worst disease attribute within the segment defines grade) • **Calcification** considered only if Severe (text); increases the within-segment grade by 1

• **IM disease (Pedal) modifier**: describes status of IM vessels (including terminal divisions of the peroneal artery) providing outflow into the foot.

*IP= Infra-Popliteal; IM=Infra-Malleolar

**The generic case of rest pain is used as a default for defining TAP, or a specific IP target artery may be selected by the clinician based on clinical circumstances (e.g. angiosome-directed).

<u>TABLE 2.</u> Description of femoro-popliteal anatomy grades.

Femoro-popliteal (FP) Grading	
0	Mild or no significant (<50%) disease
1	Total length SFA disease <1/3 (<10 cm); may include single focal CTO (< 5 cm) as long as not flush occlusion; popliteal artery with mild or no significant disease
2	Total length SFA disease 1/3-2/3 (10-20 cm); may include CTO totaling < 1/3 (10 cm) but not flush occlusion; focal popliteal artery stenosis <2 cm, not involving trifurcation
3	Total length SFA disease >2/3 (>20 cm) length; may include any flush occlusion <20 cm or non-flush CTO 10-20 cm long; short popliteal stenosis 2-5 cm, not involving trifurcation

4	Total length SFA occlusion > 20 cm; popliteal disease >5 cm or extending into trifurcation; any Popliteal artery CTO

***involvement of trifurcation means disease includes the origin of either the anterior tibial or tibioperoneal trunk

***severe calcification (e.g. >50% of circumference, diffuse, bulky, or "coral reef" plaques) within the TAP increases the within-segment **grade** by **+1**

TABLE 3. Description of infra-popliteal anatomy grades

Infra-popliteal (IP) Grading	
0	Mild or no significant (<50%) disease
1	Focal stenosis <3 cm not including TP trunk
2	Total length of target artery disease < 1/3 (<10 cm); single focal CTO (< 3 cm not including TP trunk or target artery origin)
3	Total length of target artery disease 1/3- 2/3 (10-20 cm); CTO 3-10 cm (may include target artery origin, but not TP trunk)
4	Total length of target artery disease >2/3 length; CTO > 1/3 (>10 cm) of length (may include target artery origin); any CTO of TP trunk

*IP grading is applied only to the primary selected vessel in the TAP

*****severe calcification (e.g. >50% of circumference, diffuse, bulky, or "coral reef" plaques) within the TAP increases the within-segment **grade** by **+1**.

*TP trunk disease is only included if the TAP is the posterior tibial or peroneal artery.

TABLE 4: Patterns of infrainguinal disease: assignment of overall GLASS stage for the limb based on combination of segmental (FP and IP) grades.

	INFRAINGUINAL GLASS STAGE					
FP Grade	**4**	**III**	**III**	**III**	**III**	**III**
	3	**II**	**II**	**II**	**III**	**III**
	2	**I**	**II**	**II**	**II**	**III**
	1	**I**	**I**	**II**	**II**	**III**
	0	**NA**	**I**	**I**	**II**	**III**
		0	**1**	**2**	**3**	**4**
	IP Grade					

However, because patients with diabetes now make up the majority of patients with limb-threatening ischemia, absolute perfusion is needed to be considered in the context of neuropathy, wound characteristics, and infection. In CLI patients with wounds, not only the anatomical classification of the arterial disease is required but the burden of the wound with infection status is also important and to be taken in consideration. In order to address this unmet need, the Society for Vascular Surgery (SVS) Lower Extremity Guidelines Committee created the SVS Lower Extremity Threatened Limb Classification System. This system stratifies amputation risk according to the wound, the degree of ischemia, and the presence and severity of foot infection[15]. While it may require some adjustments, WIfI scores and clinical stages appear to strongly correlate with important clinical outcomes, including those set forth in the SVS objective performance goals (OPG) that focus on limb amputation, amputation free survival, and wound healing time.

Society for Vascular Surgery Lower Extremity Threatened Limb (SVS WIfI) classification system [11]

I. Wound (W)

II. Ischemia (I)

III. foot Infection (fI)

W I fI score

W: Wound/clinical category SVS grades for rest pain and wounds/tissue loss (ulcers and gangrene): 0 (ischemic rest pain; no ulcer) 1 (mild) 2 (moderate) 3 (severe)

Table 5: Wound Assessment

Grade	Ulcer	Gangrene
0	No ulcer	No gangrene
Clinical description: ischemic rest pain (requires typical symptoms + ischemia grade 3); no wound.		
1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene
Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage		
2	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits

Clinical description: major tissue loss salvageable with multiple digital amputations or standard TMA.		
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer +/- calcaneal involvement	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis +/- calcaneal involvement
Clinical description: Extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect.		

*TMA- Trans-metatarsal amputation.

I: Ischemia

Hemodynamics/perfusion: Measure TP or TcPO2 if ABI incompressible (>1.3)

SVS grades 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

Table 6: Ischemia Grades

Grade	ABI	Ankle Systolic Pressure	TP/TcPO2
0	≥ 0.80	> 100mmHg	> 60mmHg
1	0.6-0.79	70-100mmHg	40-59mmHg
2	0.4-0.59	50-70mmHg	30-39mmHg
3	≤ 0.39	< 50mmHg	< 30mmHg

ABI- Ankle-brachial index; PVR- pulse volume recording; TP- toe pressure; TcPO2- transcutaneous oximetry.

Patients with diabetes should have TP measurements.

fI: foot Infection

SVS grades 0 (none), 1 (mild), 2 (moderate), and 3 (severe: limb and/or life-threatening)

Table 7 : Foot Infection Grades

Clinical manifestation of infection	Grade
No symptoms or signs of infection. Infection present, as defined by the presence of at least 2 of the following items: 1. Local swelling or induration. 2. Erythema > 0.5 to ≤2 cm around the ulcer. 3. Local tenderness or pain. 4. Local warmth. 5. Purulent discharge	0
Local infection involving only the skin and the subcutaneous tissue	1
Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis).	2
Local infection (as described above) with the signs of systemic inflammatory response syndrome (SIRS)	3

Amputation risk according to WIfI category

Each member of the Delphi Consensus group was asked to assign a limb threat clinical stage to each of the 64 theoretical patient combinations that would correlate with risk of amputation (stage 1 - very low; stage 2 - low; stage 3 - moderate; and stage 4 - high).

In general, risk of amputation was believed to increase as one proceeds down and to the right (increasing severity of each of the individual WIfI score components).

<u>Table 8: Amputation risk according to WIfI score</u>

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

Four classes: for each box, group combination into one of these four classes

Very low = VL = clinical stage 1
Low = L = clinical stage 2
Moderate = M = clinical stage 3
High = H = clinical stage 4
Clinical stage 5 would signify an unsalvageable foot

Based on the clinical stages and the WIfI spectrum score the major amputation risk can be estimated over one year as follows -

<u>Table 9 : WIfI clinical Stages according to score</u>

Risk of amputation	**Proposed clinical stages**	**WIfI spectrum score**
Very low	Stage 1	W0 I0 fI0,1 W0 I1 fI0 W1 I0 fI0,1 W1 I1 fI 0
low	Stage II	W0 I0 fI2 W0 I1 fI1 W0 I2 fI0,1 Wo I3 fI0 W1 I0 fI2 W1 I1 fI1 W1 I2 fi0 W2 I0 fI0/1
Moderate	Stage III	W0 I0 fI3 W0 I2 fI1,2 W0 I3 fI1,2 W1 I0 fI3 W1 I1 fI2 W1 I2 fI1 W1 I3 fI0,1 W2 I0 fI2 W2 I 1 fI0,1 W2 I2 fi0 W3 I0 fi0,1
High	Stage IV	W0 I1,2,3 fI3 W1 I1 fI3 W1 I2,3 fI2,3 W2 I0 fi3 W2 I1 fI2,3 W2 I2 fi1,2,3 W2 I3 fI0,1,2,3 W3 I0 fI2,3 W3 I1,2,3 fI0,1,2,3

Flowchart illustrating use of GLASS and WIfI for staging infrainguinal arterial disease is as follows -

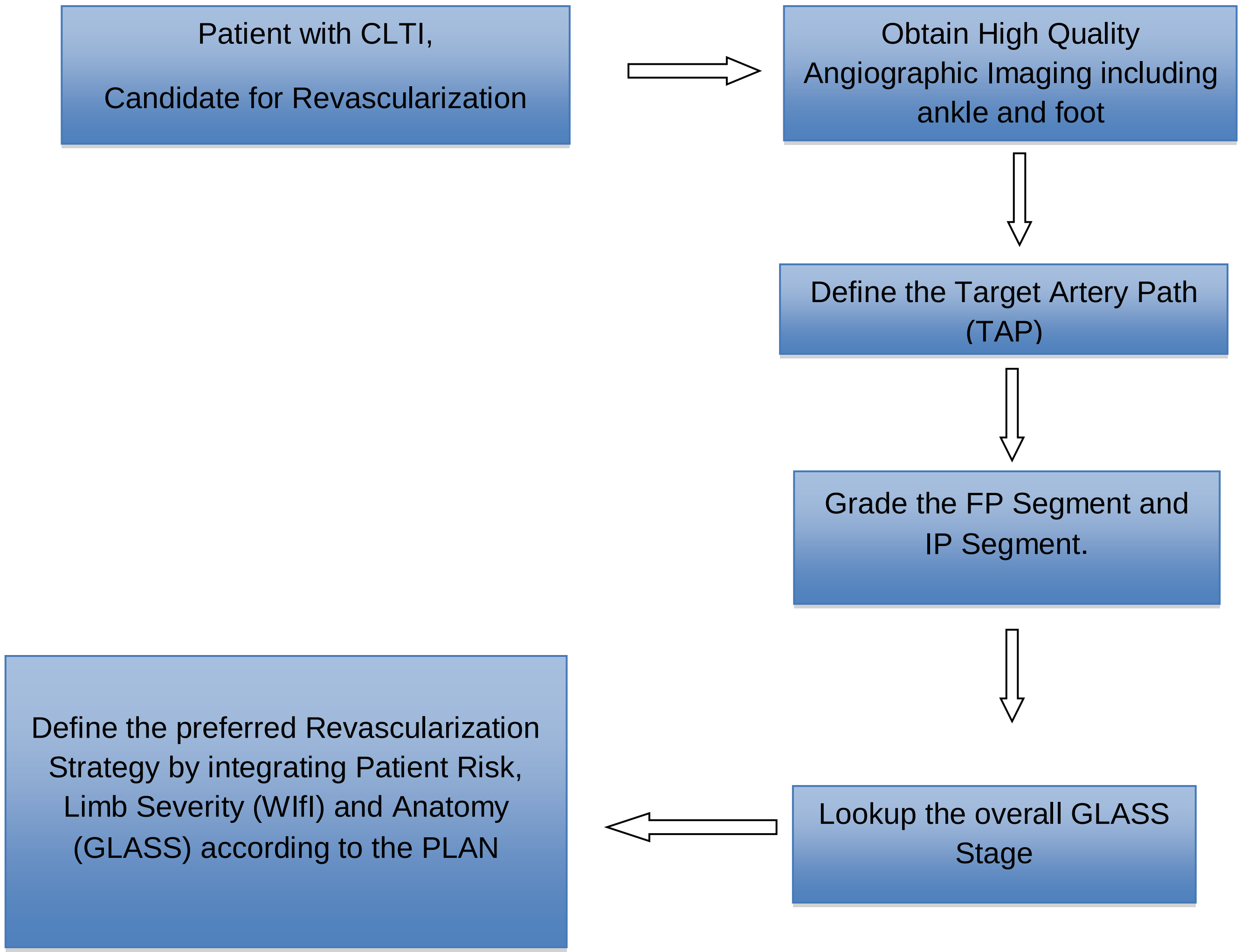

Figure 1: Flowchart of assessment of the Patient and planning for revascularization.

AIMS AND OBJECTIVES

- To classify the the infrainguinal disease of the critical limb ischemia according to femoropopliteal (FP) and tibio-peroneal (TP) segments.
- To study the limb based outcome according to new classification of new *global limb-based anatomical staging system* (GLASS) and WIfI.

MATERIALS AND METHODS

Study site

All patients presenting to Jain Institute of Vascular Sciences (JIVAS), Bengaluru, from June 2016 to June 2017 and undergoing infrainguinal revascularization procedure (bypass or plasty/stenting) for Critical Limb Ischemia(CLI) were enrolled and evaluated prospectively.

Study population

Total of 266 patients were admitted with Critical Limb Ischemia in the study period. Thirty Eight patients were excluded due to severity of disease or co morbid illness. 238 patients underwent infrainguinal revascularization procedures and these patients were followed till the end of study period (till at least 6 months).

Study design

A single center, prospective, observational and longitudinal study.

Sample size calculation

The sample size was calculated using Open Epi software at 95% confidence interval (CI). The calculated sample size was 123. Assuming 20% non response rate the estimated sample size was 123 + 24= 147. However 238 subjects were enrolled in the present study.

Time frame for study

Patients were enrolled from June 2016 to June 2017 and were followed prospectively at 1, 3 and 6 months as per study protocol.

Inclusion criteria

1. All the patients getting admitted in jain institute of vascular sciences within period with infrainguinal disease.

Exclusion Criteria:

1. Patients having aorto iliac significant disease (>50%)
2. Patients having common femoral artery stenosis (>50 %)
3. If no named artery crosses the ankle or foot.

METHODOLOGY

Patient enrollment

Demographic data of the patients was recorded with history and physical examination findings pre operatively in form of chief complaints, personal history of smoking, tobacco and alcohol if any. They were assessed for medical risk factors like diabetes mellitus, hypertension, coronary artery disease (CAD), chronic kidney disease (CKD) and cerebro-vascular disease (CVD).

In all patients' general, local examination were carried out with careful documentation of vascular status of both lower limbs along with ankle brachial index (ABI) and pulse volume recording (PVR). Preoperative imaging was based on clinical findings and was performed in the form of arterial duplex, CT angiography or MR angiography. All patients who had infrainguinal revascularization (Bypass or plasty / stenting) were enrolled for the study.

Patient Classification

Patient were then classified according to the anatomical severity of the infrainguinal arterial disease in new Global Limb Based Anatomical Staging System (GLASS). Also after clinical assessment patients were classified according to WIfI (Wound Ischemia and foot Infection) stages.

Revascularization Procedures

All patients were then decided by the operating surgeon for appropriate endovascular or bypass procedure. Post procedure patients were monitored in ICU for minimum of 24 hours. Post procedure pulse/Doppler signal status was noted and the PVR/ABI noted on the first post operative day.

Any other significant perioperative events in the form of morbidity (ACS, CIN, etc…) and mortality were also recorded.

Secondary Procedures

Patients with infected ulcers or gangrene underwent wound debridement and toe amputation following revascularisation. Depending upon the type of wound, they were either dressed with hydrocolloids or vacuum assisted device were used.

Follow up

All patients were counseled about the life style modification regarding foot ware and foot care and were regularly followed up at 1, 3 and 6 months. All enrolled patients had thorough clinical examination and

PVR/ABI surveillance at 1, 3, 6 months. Wound status of the patient in terms of healed or not healed were noted periodically.

Statistical Ananlysis

Statistical analysis was performed using SPSS, version 17.0 (SPSS, Chicago, IL). Percentages were computed based on complete data. Continuous variables were reported as mean ± standard deviation. The dependent variable for these analyses was the major amputation and limb salvage.

Ethic committee and scientific committee approval

Present study design is approved by ethic and scientific committee of Bhagwan Mahaveer Jain Hospital, Bengaluru.

RESULTS

Total 266 patients presented in the Jain Institute of Vascular Sciences (JIVAS), Bengaluru with CLI cat IV and above between June 2016 to June 2017. Twenty eight patients were excluded as no intervention was done due to either non-reconstructable disease or severe co morbidities. Two hundred and thirty eight patients were included in the study, categorized with respect to GLASS and WIfI classification. Patients underwent revascularization and followed for six months.

Total No of Patients from June 2016-2017 : 266 of infrainguinal disease				
In The Study included : 238			Excluded : 28*	
Months	**Major Amputation**	**Death (Cardiac)**	**Lost for Follow up**	**Total No.**
0---1	**6**	**4 (2)**	**4**	**224**
2---3	**16**	**12 (7)**	**9**	**187**
4---6	**4**	**8 (3)**	**7**	**168**

Consolidated Standards of Reporting Trials (CONSORT) Diagram

*= 15 patients were having extensive non-reconstructable disease, 4 patients had pre operative MI hence cancelled, 9 patients managed conservatively due to their severe co morbidities.

AGE GROUP :

Table 10: Age Group of patients

Age group	Frequency	Percentage
31-40	15	6.3%
41-50	13	5.4%
51-60	58	24.3%
61-70	77	32.3%
71-80	61	25.6%
81-90	9	3.7%
91-100	5	2.1%
total	238	100%

Mean age of the patient: 63. 4 yrs with Std. deviation 12.1.

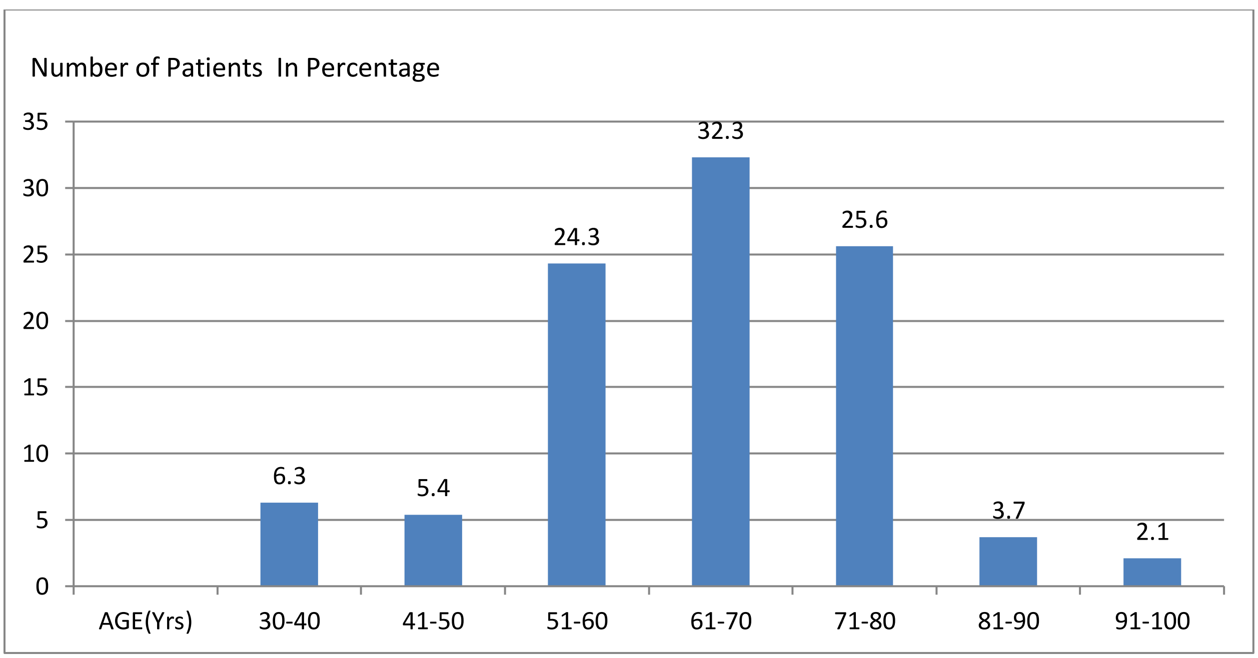

Figure 2: Age Groups.

82.2% patients belonged to the age group of 51 to 80 Years.

GENDER DISTRIBUTION :

Table 11 : Gender Distribution

	Numbers	Percentage
Males	196	82.35
Females	42	17.7

Study patients were predominantly males.

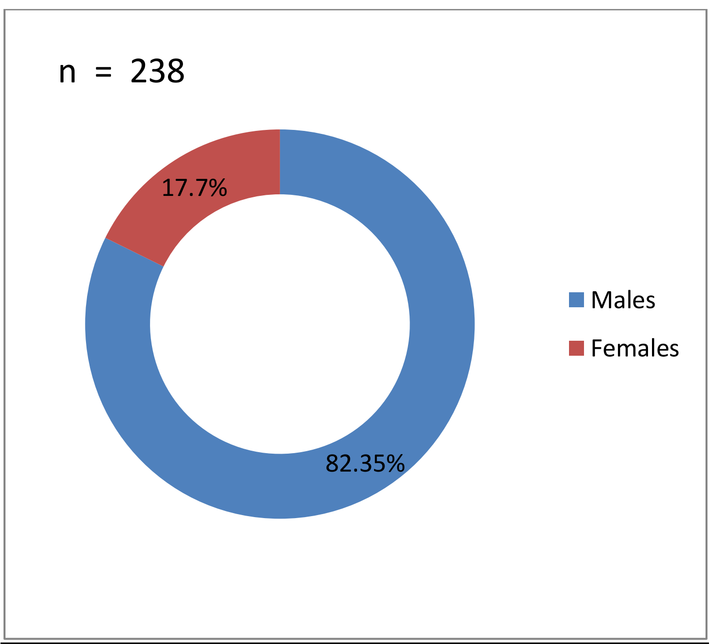

Figure 3: Gender Distribution

TOBACCO USE:

Table 12 : Tobacco Use

Tobacco Use	Numbers	Percentage
Yes	145	60.9
No	93	39.07
Total (n)	238	

More than 50% of the patients were having present or past history of the tobacco use.

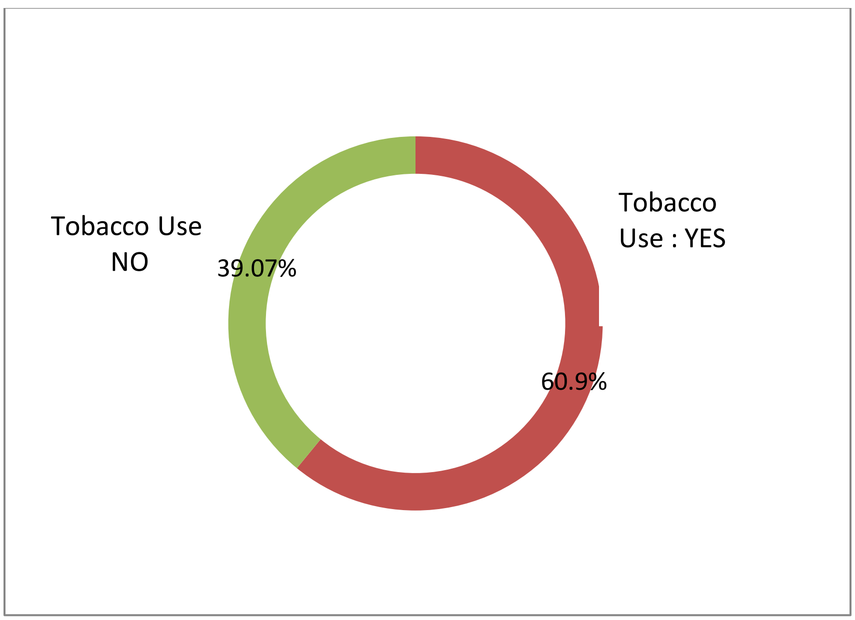

Figure 4: Tobacco Use

CO-MORBIDITIES:

On analyzing the comorbidities, 78.15% were diabetics, 66.8% were hypertensive, 21.55% were suffering from chronic kidney diseases, 39.9% of patients were having CAD, 34.87 % were having history of dyslipidemia. 12.18% diagnosed to have CVD and 9% patients were known COPD cases.

Table 13 Comorbidities:

Comorbidities	Number	Percentage
DM II	186	78.15
HTN	159	66.8
CKD	61	21.55
CAD	95	39.9
Dyslipidemia	83	34.87
CVD	29	12.18
COPD	21	9

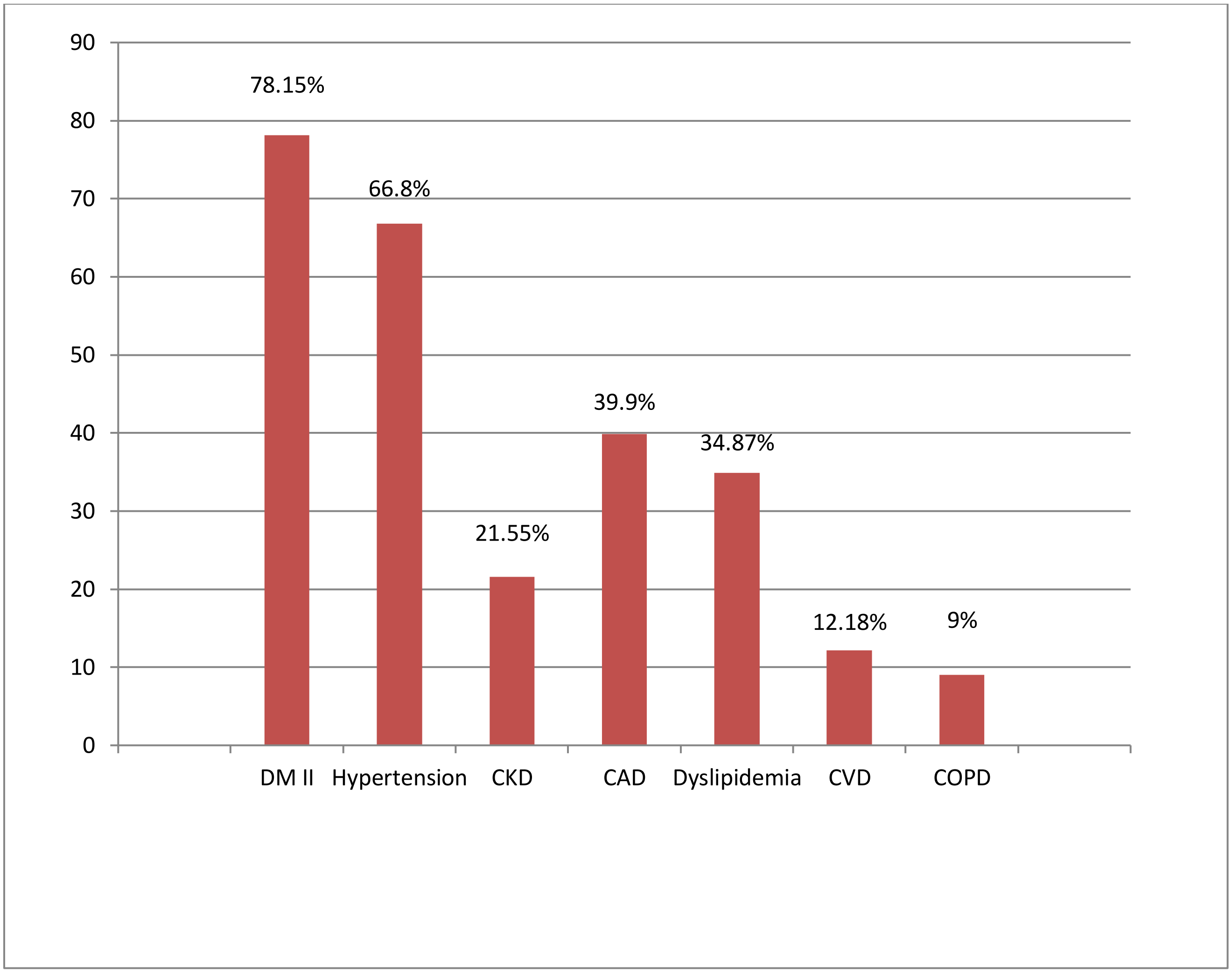

Figure 5 : Comorbidities

Table 14 : RUTHERFORD BECKER CATEGORY:

Only patients with Rutherford category IV or more were selected. More than 60% of patients were falling in Rutherford Category VI.

Rutherford Category	Numbers	Percentage
Cat IV	21	8.82 %
Cat V	55	23.1 %
Cat VI	162	68.6 %
Total(n)	238	

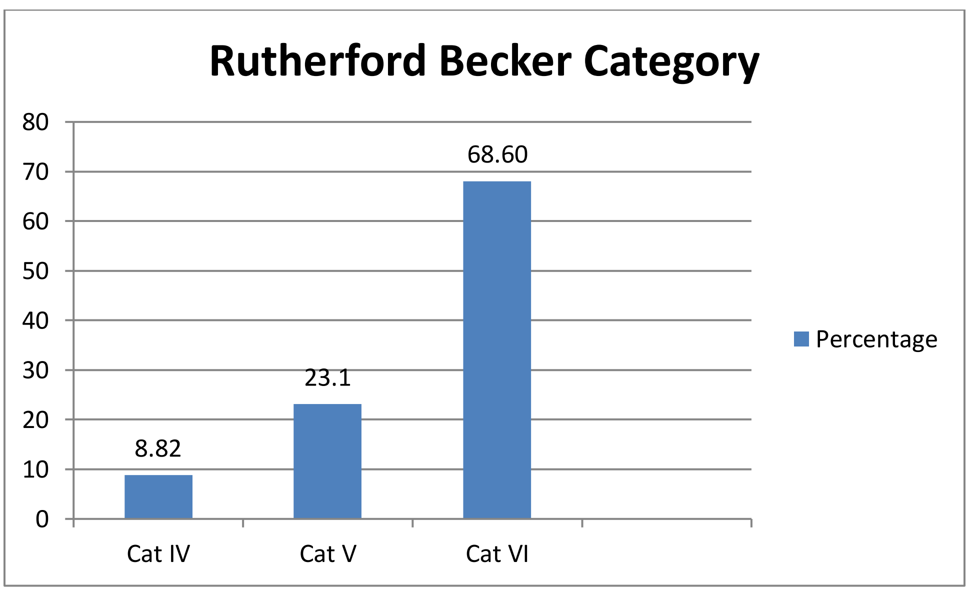

Figure 6: Rutherford Becker Category

Table 15: GLASS staging:

All the CLI patients in the study were categorized according to new GLASS classification and staged accordingly. More than 60% of the patients were of GLASS stage II followed by Stage I and lastly stage III.

GLASS Stage	Numbers	Percentage
I	68	28.57 %
II	145	60.90 %
III	25	10.50 %
Total(n)	238	

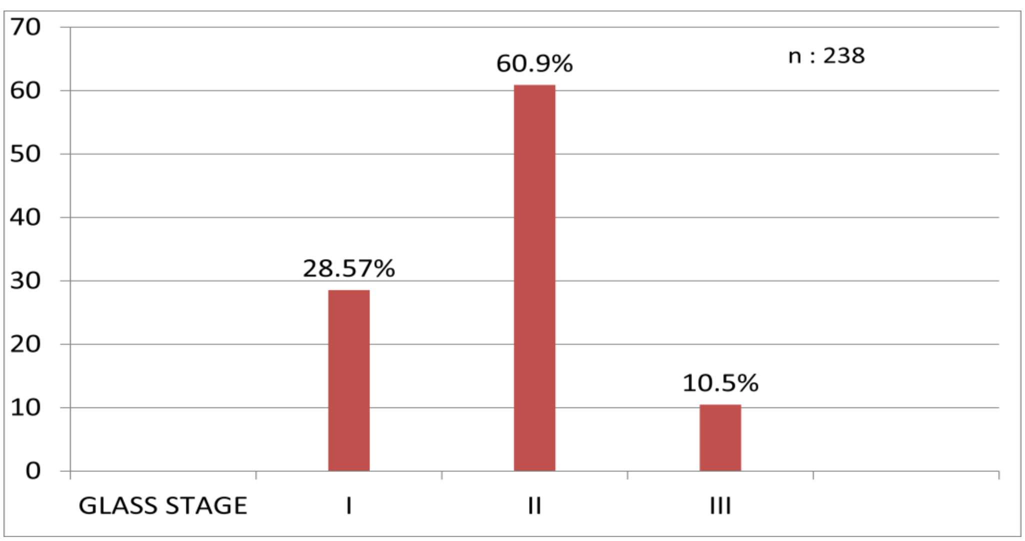

Figure 7: GLASS STAGE Categorization

Pre Op WIfI SCORES

All patients were categorized according to WifI classification and staged accordingly. More than 70% patients were in stage III or Stage IV.

Table 16: Pre Op WIfI SCORES

WIfI Stage	Number	Percentage
I	6	2.52 %
II	43	18.60 %
III	92	38.60 %
IV	97	40.70 %
Total	238	

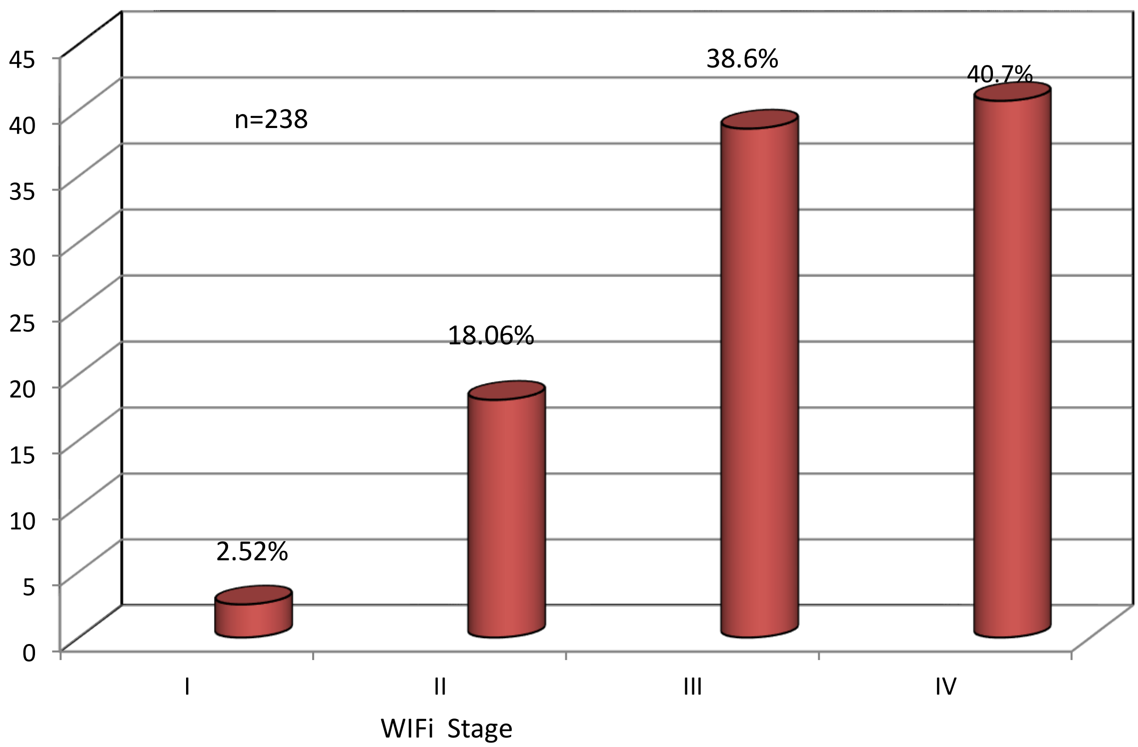

Figure 8: WIfI Stage Categorization

OPERATIVE ANALYSIS

Out of selected 238 patients 192 patients underwent total angioplasty procedures, 51 patients underwent arterial bypass and 5 patients underwent hybrid procedures. Further analysis of angioplasty and the bypass procedures are as follows.

Table 17: Endovascular Procedures

Angioplasty	Number	Percentage
SFA	39	20.31 %
Infrapopliteal	107	55.72 %
multilevel	46	23.95 %
Total	192	

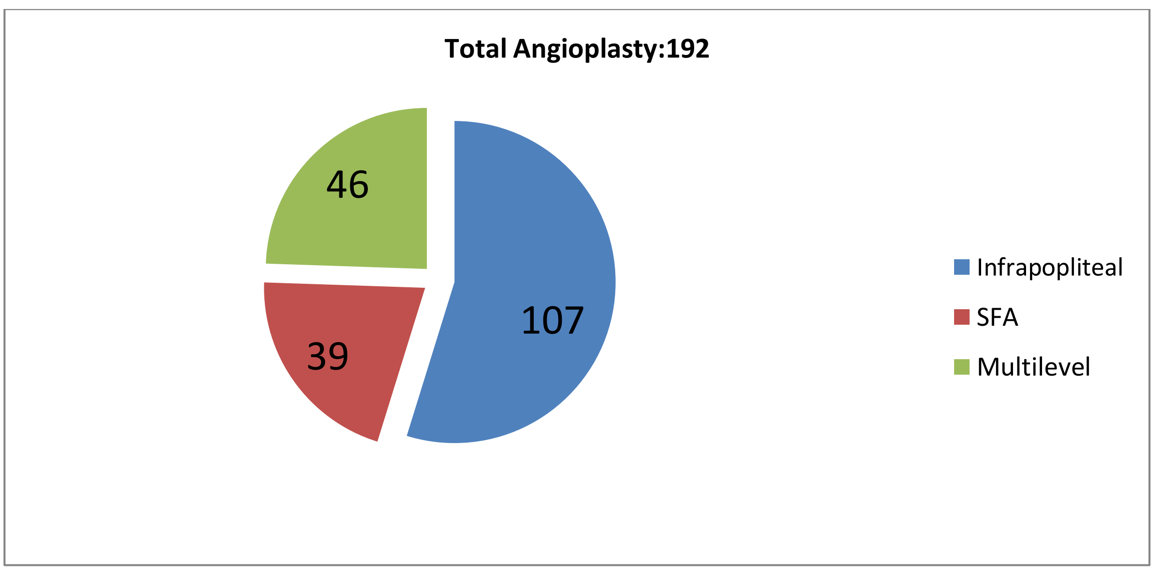

Figure 9 : Endovascular Procedures

Table 18 : Bypass Procedures

Bypass	Number	Percentage
Fem pop vein	15	29.41 %
Fem pop graft	28	54.90 %
Fem distal	8	15.68 %
Total	51	

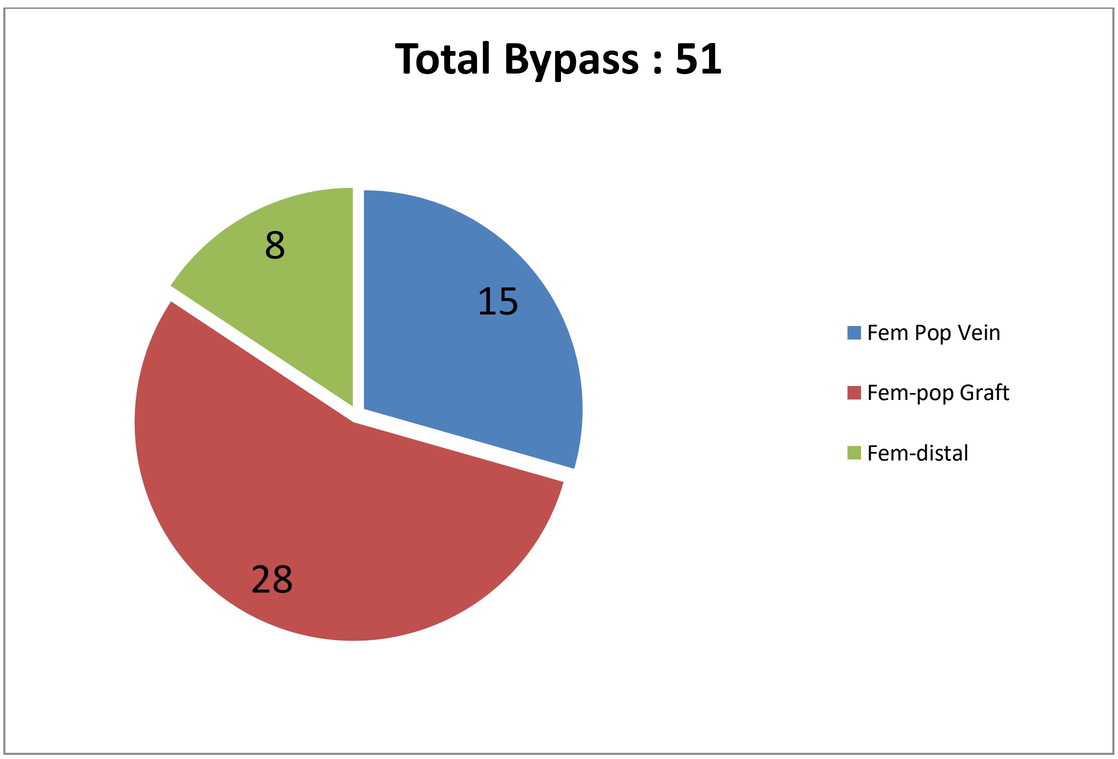

Figure 10: Bypass procedures and analysis

WOUND HEALING RATE

Total number of patients followed were 238. Twenty one patients were having rest pain without wound. 26 patients undwerwent major amputations at the end of six months. Six patients' wounds were not healed at the end of 6 months. Seven patients were lost to follow up and 11 patients died in six months. 159 patients were followed till the wound healed. Maximum number of wounds healed were between 1-3 months. The mean wound healing time was 2.96 months with standard deviation of 0.9 months.

Table No. 19 : Wound Healing Rate

Wound Healing Rate in Months	Number of patients
0--1	6
2--3	84
4--6	69
>6	6

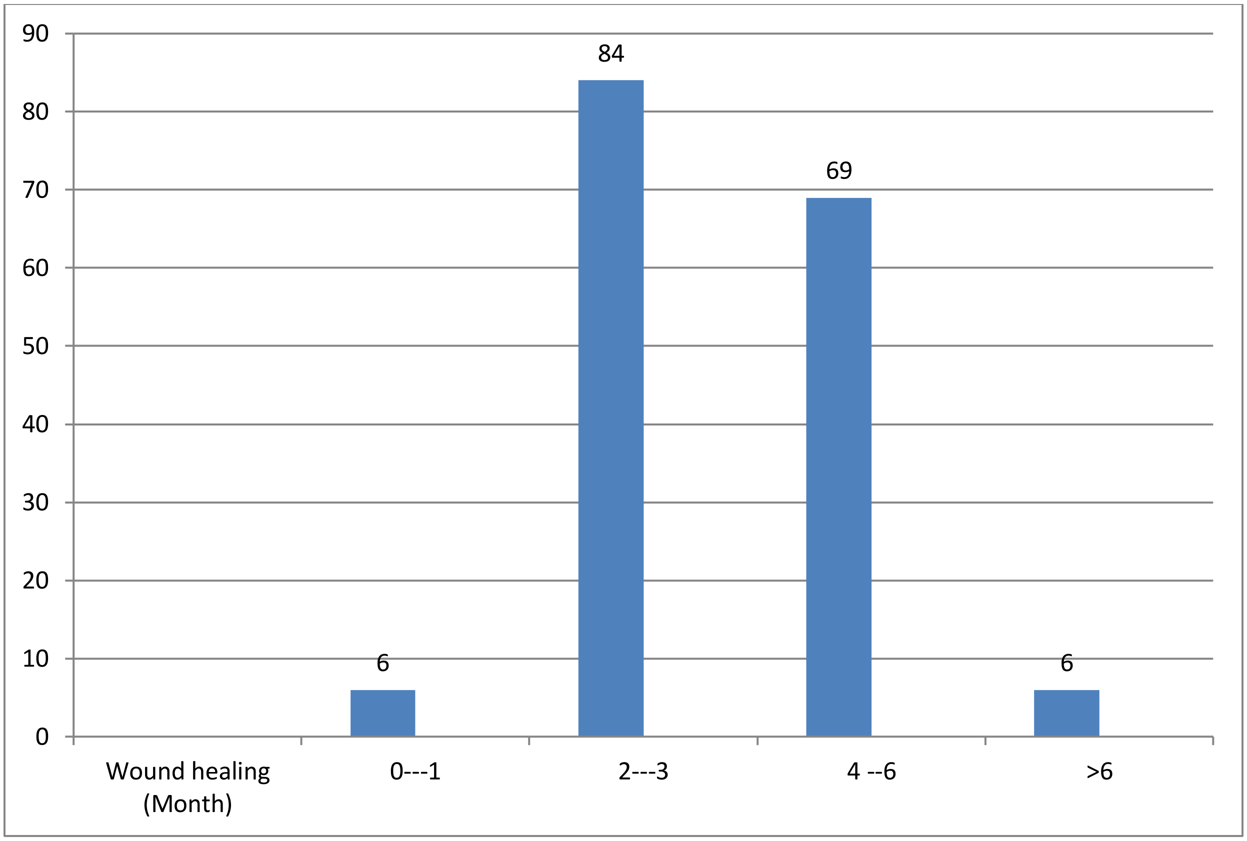

Figure 11: Wound Healing Rate

Major Amputations According to GLASS and WIfI Classification

Total number of major amputations was 26 in six months. The statistical month wise analysis according to GLASS and WIfI classifications are as follows. There were no major amputations noted in stage I and Stage II in WifI. Also maximum amputations were noted in WIfI stage IV. According to GLASS classification maximum number of amputations were noted in Stage II.

Table No. 20: Major Amputations with GLASS and WIfI Classifications

STAGE	GLASS I	II	III
WIfI I	0	0	0
II	0	0	0
III	3	7	1
IV	5	8	2

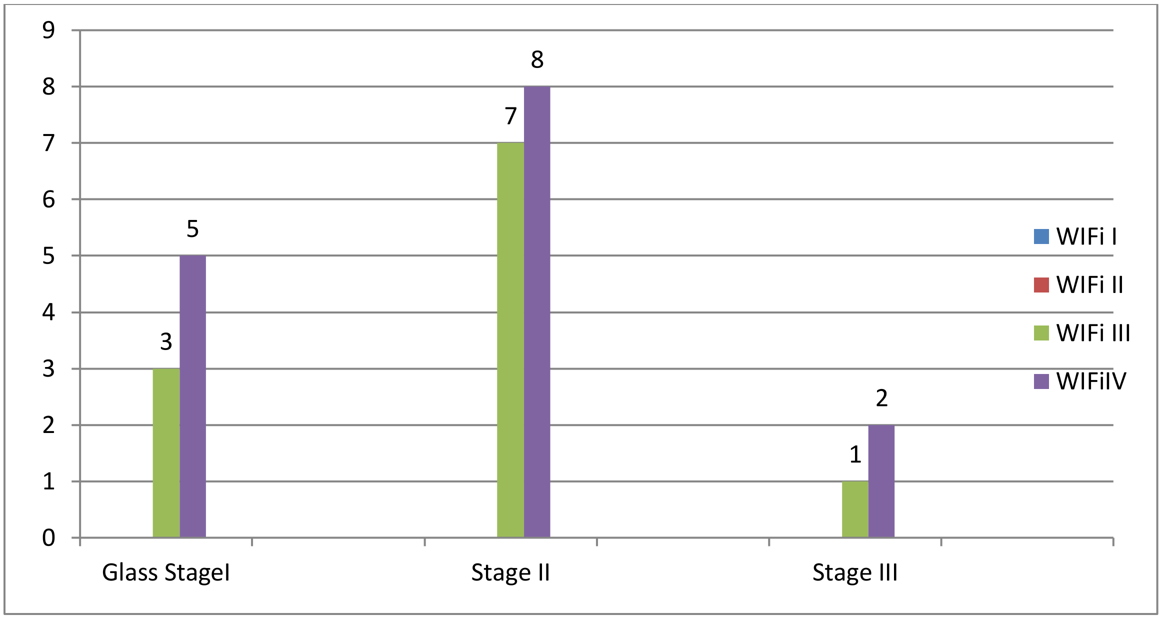

Figure 12: Major amputations according to GLASS and WIfI classification

LIMB SALVAGE RATES IN GLASS CLASSIFICATION

At the end of six months the limb salvage rate in GLASS stage I was 83.3%, in stage II was 87.37% and in stage III was 82.35%.

Table 21: Limb salvage in GLASS classification

	1st month %	3rd month %	6th month %	**Overall**
STAGE I	100	87.5	83.3	**83.3**
STAGE II	96.11	89.32	87.37	**87.37**
STAGE III	94.11	82.35	82.35	**82.35**

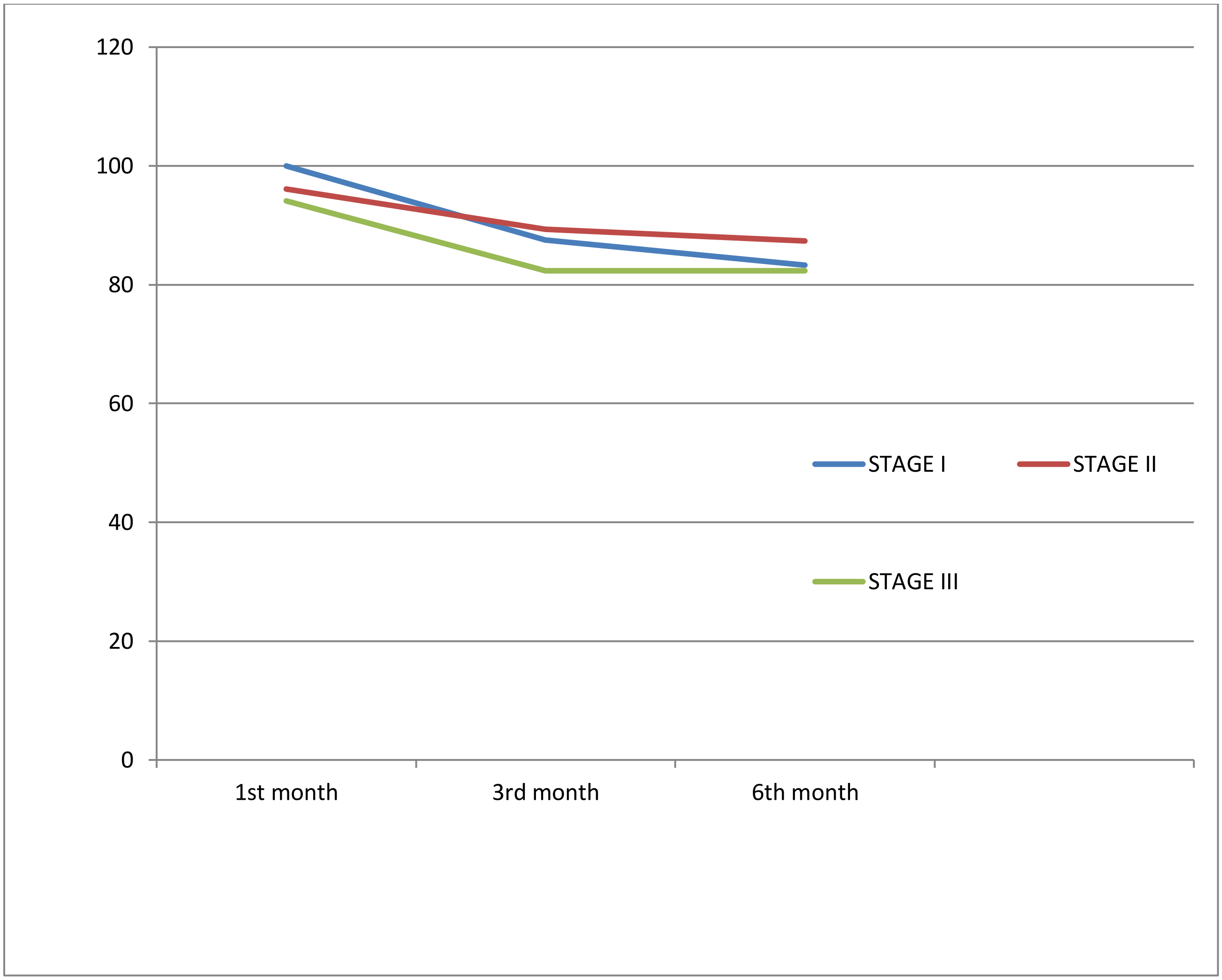

Figure 13: Limb Salvage rate according to GLASS classification

LIMB SALVAGE RATE IN WIfI CLASSIFICATION

There were no amputations noted in WIfI stage I and II in six month follow up.

Limb salvage rate in stage III was 85.29% and in stage IV was 78.12%.

Table 22: Limb salvage according to WIfI classification (%)

	1ST MONTH	3RD MONTH	6^{TH} MONTH	OVERALL
STAGE I	100	100	100	**100**
STAGE II	100	100	100	**100**
STAGE III	98.86	89.18	85.29	**85.29**
STAGE IV	95.5	83.7	78.12	**78.12**

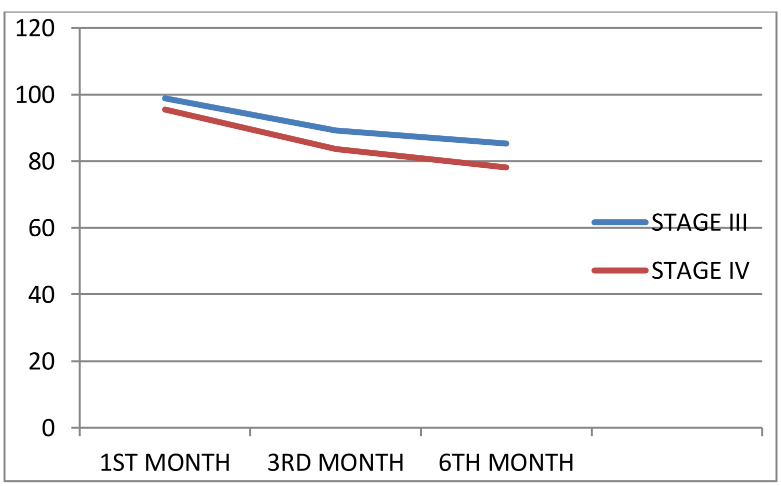

Figure 14: Limb Salvage rate according to WIfI classification.

DISCUSSION

In this prospectively conducted study at JIVAS from June 2016 to June 2017 we categorized our patients who admitted with infrainguinal disease, according to GLASS and WIfI classification. Patients underwent infrainguinal revascularization and were followed for six months. We calculated clinical outcomes in terms of wound healing and limb salvage.

To the best of our knowledge there is no study which has classified the infrainguinal disease according to GLASS classification. Very few studies have actually included WIfI classification and none in India. This prospective study will give us an idea about the limb vascularity and wound burden together.

In our institute, 238 patients underwent infrainguinal revascularization for CLI between months of June 2016 to June 2017, and all patients were chosen for the study after calculating the sample size by EPI info software. At the end of the six months 20 patients were lost to follow up and 24 patients died.

DEMOGRAPHICS

Mean age of our patients was 63. 4 yrs with Std Deviation of 12.1.More than 80% of patients were between the age group of 51 to 80 years. Male to female ratio was

196: 42 (82.35 % vs 17.6 %). Studies done by **Cull et al** [23]**, William Robinson et al** [24]**, Bala Ramanan et al** [25] also had predominantly male population.

COMORBIDITIES

In our study, 78.15% were diabetics, 66.8% were hypertensive, 21.55% were CKD, 39.9% of patients were suffering from CAD, 34.87% were having history of dyslipidemia while 12% were previously diagnosed to have CVD and 9% patients were known COPD cases. Diabetes and HTN were predominant comorbidities seen in our study group patients. Similar results noticed in other studies also.

Table 23: Comparison of co-morbidities with other studies

Comorbidities	JIVAS No (%)	Mathioudakis et al [26]	Ramanan et al[25]	Cull et al[23]	Robinson et al[24]
DM II	186(78.15)	206(94.9)	118(75)	91(66)	163(83.7)
HTN	159(66.80)	177(81.6)	132(85)	130(93)	229(89)
CKD	61(21.55)	39(18)	37(24)	19(14)	184(72)
CAD	95(39.90)	51(23.5)	75(48)	87(3)	115(45)
Dyslipidemia	83(34.87)	106(48.9)	111(71)	99(71)	190(74)
CVD	29(12.18)	17(7.8)	--	--	35(14)
COPD	21(9)	23(10.6)	20(13)	--	36(14)

Diabetes was more common in Mathioudakis et al where as Dyslipidemia was commonly seen in Ramanan et al, Cull et al and Robinson et al studies.

Pre-op Rutherford Categories

In our study only Rutherford category IV and above were selected. Numbers of patients with Rutherford Category IV were 21(8.82%), category V were 55(23.1%) and Category VI were 162(68.60%). This also reflects that patients getting admitted in our department with infrainguinal disease predominantly have major tissue loss.

Pre-op GLASS and WIfI classification

All the patients admitted in JIVAS were classified as per GLASS and WifI classification system. Out of total 238 patients, 68 (28.57%) were in Stage I of GLASS classification, 145(60.9%) were in stage II and 25(10.5%) were in stage III. All the 68 Patients of Stage I underwent angioplasty. In Stage II, 111 patients underwent angioplasty and 29 patients underwent bypass surgery. In Stage III, 8 patients underwent angioplasty and 17 patients underwent bypass. Five Patients underwent hybrid procedures.

In WIfI classification only 6 (2.52%) patients presented with WIfI stage I, 43 (18.6%) in WIfI stage II, 92 (38.6%) in WIfI stage III and 97 (40.7) in WIfI stage IV. Cull et al [23], Zhan et al [27], Darling et al [31] and other studies also noted very less patients in WIfI stage I and large number of patients presented in Stage III or IV as follows.

Table 24: Comparision of Stage of Presentation According to WIfI

Study(Yr):Number Of limbs at risk	Stage 1 No(%)	Stage 2 No(%)	Stage 3 No(%)	Stage 4 No(%)
JIVAS Study:238	6(2.52)	43(18.6)	92(38.6%)	97(40.7)
Zhan et al [27] (2015):201	39(19.4)	50(24.8)	53(26.3)	59(29.3)
Cull et al [23] (2014):151	37(24.5)	63(41.7)	43(28.4)	8(5.2)
Causey et al [28] (2016):160	21(13.1)	48(30)	42(26.2)	49(30.62)
Beropoulis et al [29] (2016):126	29(23)	42(33.3)	29(23)	26(20.6)
Ward et al [30] (2017):98	5(5.1)	21(21.4)	14(14.2)	58(59.1)
Darling et al [31] (2017):992	12(1.2)	293(29.5)	249(24)	438(43)
Robinson et al [24] (2017):280	48(17.14)	67(23.9)	64(22.8)	83(29.6)
Tokuda et al [32] (2017):163	16(9.81)	30(18.4)	56(34.3)	61(37.4)

Wound healing at 6th month

Out of total 238 patients, 21 patients were having rest pain and hence excluded. Twenty six patients underwent major amputation. Forty two patients underwent re-debridement and minor amputations after revascularization. Total of 159 limbs were followed till six months. Out of 159 patients 6 (3.63%) patients' wound healed within one month, 84 (50.9%) patients' wound healed between 1 to 3 months and 69 (41.8) patients' wound healed between 3 to 6 months. The mean wound healing rate in this study was 2.96 months with standard deviation of 0.9 months. Ramanan et al [25] showed the average duration of foot wound to heal at rate of 3.5 months. Mathioudakis et al [26] revealed average wound healing time of around 4.1 months. Similarly average wound healing time in Cull et al [23] study was 2.7 month.

Limb Salvage

Limb Salvage according to GLASS Classification. All the patients followed up till 6 months. Patients who underwent major amputations (above knee or below knee amputations) were considered as failure. In Stage I the overall limb salvage rate at the end of six month was 83.3%, in stage II it was 87.37% and in Stage III it was 82.35%. There was no significant difference in the amputation rates of

GLASS stage I, stage II and stage II. The maximum number of major limb amputation was found in GLASS stage II because more number of patients were present in this category.

Limb salvage rate in WIfI classification differs than the GLASS classification. There were no amputations in WIfI Stage I and II. In WIfI stage three 85.29% was the limb salvage rate and in stage IV it dropped to 78.12%. According to this classification limb salvage rate decreases as the stage increases. Number of other studies also observed similar findings.

Table 25 : Comparison Of Limb Salvage Rates As per WIfI Classification

STUDIES	LIMB SALVAGE RATES (%) IN WIfI STAGE			
	STAGE I	STAGE II	STAGE III	STAGE IV
JIVAS	100	100	85.29	78.12
Cull et al [23]	97.3	88.9	76.7	62.5
Ramanan et al [25]	92	81	93	63
Robinson et al [24]	96	84	90	78

CONCLUSION

Peripheral arterial disease is a growing health problem, especially in diabetic and CKD patients. Any patients presenting with the non healing wound or toe gangrene comes under the category of critical limb ischemia. The primary aim of the vascular specialist is to make the patient wound free by revascularization. Although surgical bypass is the gold standard in these patients, recent advances in the endovascular technology and hardware for endovascular intervention led to be the first revascularisation option for older patients with multiple co- morbidities.

To address the disease correctly one should know the burden of the disease. Present classification of the infrainguinal arterial disease (TASC, Bollinger, Graziani) don’t give the complete picture of infrainguinal arterial disease hence the new GLASS grading system for the infrainguinal arterial disease has been designed which not only stages the limb according to the severity of the disease (stenosis or occlusion) but also acts as guide to create the in-line flow across the foot (either by bypass or endovascular procedure).

Apart from the diseased infrainguinal arterial segments we found that the burden of the wound is also equally important. The Lower Extremity Guidelines Committee of the Society for Vascular Surgery (SVS) recently proposed the Lower Extremity

Threatened Limb Classification System (Wound, Ischemia, foot Infection [WIfI]) to stratify the risk of limb amputation in a heterogeneous population of patients presenting with critical limb ischemia (CLI) . We performed the prospective study on patients presenting with critical limb ischemia and classified them according to GLASS and WIfI classification. After following the patients for six months we conclude that there is not much difference in the Limb salvage rates in GLASS stages, but as the WIfI stage increases the limb salvage decreases. So wound burden and Infection in the lower limb plays a major role for limb salvage apart from ischemia.

SUMMARY

Lower Limb Outcome in Critical Limb Ischemia for infrainguinal arterial disease (SFA and distal) based on Global Limb based Anatomic Staging System (GLASS).

A prospective nonrandomized single center study was conducted at Jain Institute of Vascular Sciences (JIVAS), Bengaluru with aim to classify the patients of lower limb critical ischemia according to new GLASS classification. Also patients were staged with wound infection and limb ischemia status.

To summarize we enrolled 238 patients. All patients were categorized according to GLASS and WIfI classification. All patients underwent revascularization procedures in terms of either open bypass or endovascular procedure. Patients also underwent secondary procedures like debridement or minor toe amputations with revascularization. All patients were then followed up for minimum period of six months.

After classifying the patients according to new GLASS classifications we found that maximum patients fall in stage II with moderate infrainguinal arterial disease followed by stage I and lastly Stage III. Also there is not much difference in the limb salvage rates in GLASS stage though maximum limb salvage rate is in GLASS stage II i.e. 87%.

According to WIfI classification, we found that most of the patients present with large wound burden or severe infection. Around 78% (182) patients presented in stage III and stage IV of the WIfI Grade. We also noticed that as the WIfI stage increases the limb salvage rate decreases significantly.

DEFINITIONS

Diabetes Mellitus was defined as baseline fasting blood glucose levels of >126mg/dl, HbA1c (>6.5%) or the need for glucose lowering treatment according to World Health Organization Criteria [33].

Hypertension was defined as having high blood pressure (systolic blood pressure > 140 mm Hg and / or diastolic blood pressure >90 mm Hg) and/or receiving antihypertensive treatment for at least 1 year before inclusion of the study [34].

Coronary Artery Disease was defined as a history of angina pectoris, myocardial infarction, congestive heart disease, or prior coronary artery revascularizations [35].

Chronic Kidney Disease was defined as serum creatinine >1.5 mg/dl 24 hours before surgery [36].

Smoking habit was defined as active smoker when the patient smoked at the time of the inclusion or gave up the habit in a period lower than 6 months [37].

Limb Salvage was defined as prevention of major amputation. Major amputation was defined as limb loss below or above knee level, while minor amputation was defined as transmetatarsal or more distal level amputation of the lower extremity[38].

Acute Coronary Syndrome refers to group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST segment elevation myocardial Infarction (NSTMI), and ST- segment elevation myocardial Infarction{STEMI) [39].

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