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Original Research Article

Systemic inflammatory response syndrome as a predictor of poorer outcomes in diabetic foot infection: a prospective analytical study

Anand Vinay Karnawat[1], Vijayakumar Chellappa[1], Balasubramanian Gopal[1]*, Rajkumar Nagarajan[1], Krishnamachari Srinivasan[2]

[1]Department of Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India
[2]Department of Surgery, Sri Manakula Vinayagar Medical College and Hospital, Puducherry India

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***Correspondence:**
Dr. Balasubramanian Gopal,
E-mail: drbala18@gmail.com

ABSTRACT

Background: This study was done to diagnose the severity of infection in a group of hospitalized diabetic foot infection (DFI) patients based on the presence or absence of systemic inflammatory response syndrome (SIRS) and compare the outcomes.
Methods: This was a single-center cohort study, in which 50 consecutive DFI patients having SIRS and 50 consecutive patients not having SIRS were included. Patients were followed for the duration of the hospital stay; parameters for glycaemic control, minor and major amputation, microbial culture, duration of hospital and ICU stay and mortality was recorded.
Results: The relative risk of major amputation among the patients of DFI who presented with SIRS was 2.66 times higher compared to who was not having SIRS at presentation (95% CI, 1.56-4.55). The presence of polymicrobial infection also had a statistically significant association with the incidence of major amputation. The duration of hospital stay was ~9.5 days longer in the DFI patients who presented with SIRS compared to who was not having SIRS at the time of presentation [8.00 (4.00-20.50) days versus 17.50 (10.75-38.25) days]. DFI patients with SIRS required a significantly prolonged ICU.
Conclusions: SIRS can be used as objective criteria to predict poorer outcomes in the diabetic foot infection patient and also to classify it.

Keywords: DFI, Morbitity, Sepsis, SIRS, Quality of life

INTRODUCTION

Diabetes mellitus has been a global epidemic of 21st century. In 2015, International Diabetes Federation (IDF) published its seventh atlas, which estimated that 415 million people among the adults of age group 20-79 years worldwide are suffering from diabetes mellitus. Which amounts to 8.8% of adults aged between 20-79 years of age. One in eleven adults is suffering from diabetes mellitus. Taking ongoing trends into consideration IDF predicted by 2040, 642 million people worldwide will be diabetic. India is house for 69.2 million diabetics. It ranks second in the absolute number of diabetics following China at first place. [1]

Most dreaded complication of diabetes mellitus is lower extremity amputations. Patients who are undergoing lower extremity amputation will require ipsilateral or contralateral amputation within next three to five years. Five-year mortality related to diabetic foot ulcer is very high. According to Moulik et al, five-year mortality rate for patients with diabetic foot ulcer is 45%, 18% and 55%

for neuropathic, neuro- ischemic and ischemic ulcers, respectively. Five years mortality rate after major amputation in patients with diabetes mellitus reaches up to 50%. Mortality associated with lower extremity complications of diabetes mellitus and amputation is more than or at least comparable to the most common cancers. In few high-risk subgroups like patients with chronic kidney disease it can reach up to 90%.[2] Almost 85% of all the lower extremity amputations are preceded by an ulcer. Usually it follows a characteristic sequence of events of neuropathy, ulcer, and progressive infection leading to amputation. Amputations due to non-ischemic condition is a situation which could have been prevented by early and adequate treatment of an ulcer.[2,3]

It is important to have a classification system for diabetic foot infection to formulate standard treatment plan, to communicate between the caregivers, to monitor the progress of the disease, predict outcomes and allocate limited resources available with healthcare system properly. This can help in understanding natural history of the diabetic foot and further our knowledge about it. Wagner-Meggit classification is one of the very first system of classification of the diabetic foot.[4] As our insight in the pathophysiology of foot problems in diabetes is deepening, after the advancement of this classification many modifications of it have been devised and many more new classifications have been proposed. Most of these classification systems take into account only the local wound condition. These classification systems fail to take into account systemic component of diabetic foot infection (DFI).

Using infection part of PEDIS classification system proposed by IWDGF for research purpose, IDSA modified its classification of diabetic foot infection. Presence of SIRS was used as the criteria to differentiate severe diabetic foot infection from moderate diabetic foot infection. Systemic inflammatory response syndrome (SIRS) represents the systemic derangement caused by DFI. But, this classification has never been validated in any prospective study.

METHODS

This study was designed to be a prospective analytical study. It was conducted in a tertiary care centre in South India for a period of one year (January 2017 to December 2017).

Inclusion criteria

Patients having DFI and admitted for the same in surgery wards.

Exclusion criteria

Patients who were already treated surgically for DFI in the other hospital or who were referred from the other hospital.

Informed consent was obtained from all individual participants included in the study.

Sample size

Wukich et al, in their retrospective study reported major amputation rate of 5% and 26% in patients with moderate diabetic foot infection (SIRS absent) and severe diabetic foot infection (SIRS present), respectively.[5] Assuming alpha error of 5%, power of 80%, expected percentage of participants requiring major amputations in moderate and severe group as 5% and 26%, respectively, the required sample size is 46 in each group. Considering drop out from study at 10% we will include 50 patients in each group.

Study procedure

Presence of SIRS was recorded when two out of four below mentioned criteria were present, at the time of admission in a patient with DFI:[6]

- Temperature above 38° C or below 36° C.
- Heart rate above 90 beats per minute
- Respiratory rate above 20 breaths per minute
- WBC count above 12000 cells per mm^3 or below 4000 cells per mm^3

Fifty consecutively admitted DFI patients not having SIRS (Group 1) and 50 consecutive DFI patients having SIRS (Group 2) were included in the study, making total study population of 100 patients.

Basic demographic variables (name, age, sex, address) were recorded. Variables associated with the diabetic status (duration of diabetes mellitus, treatment patient was receiving for diabetes mellitus, adherence to the treatment regimen) were recorded. Co-morbidities other than diabetes mellitus were also recorded.

Wound status at the time of admission was recorded using University of Texas San Antonio (UTSA) classification.[7] To determine the presence of limb ischemia, pulse was examined in the dorsalis pedis, anterior tibial and posterior arteries of the same limb using hand held Doppler. If any of the pulse was not recorded with Doppler, presence of limb ischemia was recorded. If all the pulses in the foot were recorded with the Doppler, then Ankle-Brachial Pressure Index (ABPI) was recorded. Patients having ABPI<0.8 were labelled as having limb ischemia. At the time of admission, tissue bit from the wound was sent for aerobic bacterial culture and antibiotic sensitivity. Next morning after admission, fasting blood sugar (FBS) and postprandial blood sugar (2 hours) (PPBS) was recorded.

During the hospital admission, patients were managed according to the respective unit protocol. Decision of major amputation was taken by the consensus of two independent consultants. Decision regarding minor

amputation was taken by the consultant of the respective unit. Decision regarding discharge of patient was taken by the respective unit under which patient was admitted.

At the time of discharge, duration of the hospital stay, duration of the ICU stay and if patient required amputation during the hospital stay, it was recorded. Any amputation distal to the tarso-metatarsal joint was recorded as a minor amputation and amputation proximal to the tarso-metatarsal joint was recorded as a major amputation.

Statistical analysis

Continuous variables which were following normal distribution (age, duration of diabetes mellitus, FBS, PPBS were expressed using mean and standard deviation and compared using unpaired t test. Continuous variables which were not following normal distribution (duration of the hospital stay and duration of ICU stay) were expressed as median and interquartile range and compared using Mann-Whitney U test. Categorical variables (sex, co-morbidities, SIRS, limb ischemia, wound status, poly-microbial infection, minor amputation, major amputation and mortality) were compared using Chi-square test. Statistical analysis was done using SPSS software V.18.

RESULTS

In this prospective study, two groups of patients with DFI, based on presence or absence of SIRS at the time of admission were compared. Both the groups were homogeneous with regard to age, duration of diabetes mellitus, modality of treatment patients receiving for diabetes mellitus, co-morbidities and presence of limb ischemia (Table 1 and 2).

Table 1: Comparison of demographic variables and co-morbidities.

Parameters	Group 1 (No SIRS)	Group 2 (SIRS)	P value
Age (years) (mean±SD)	54.74±10.31	54.84±11.69	0.964
Gender N (%)			
Male	35 (70)	27 (54)	0.001
Female	15 (30)	23 (46)	
Comorbidities N (%)			
No	35 (70)	30 (60)	0.393
HTN	6 (12)	7 (14)	
CKD	6 (12)	8 (16)	
HTN and CKD	0 (0)	3 (6)	
IHD	3 (6)	1 (2)	
HTN and IHD	0 (0)	1 (2)	
Limb ischemia N (%)	22 (44)	19 (38)	0.542

With regard to the gender distribution, the group of participants with SIRS had a proportionately higher percentage of female participants compared to the group of participants without SIRS (46% versus 30%). This can be attributed to neglect towards women's health care which had been seen in the Indian population, leading to late presentation to the hospital.

Table 2: Comparison of duration of DM, treatment modality for DM and blood sugars.

Parameters	Group 1 (No SIRS)	Group 2 (SIRS)	P value
Mean duration of DM (years) (mean±SD)	8.74±6.45	8.55±5.37	0.871
Treatment modality for DM N (%)			
No treatment	4 (8)	3 (6)	0.502
OHA	21 (42)	25 (50)	
Insulin	7 (14)	10 (20)	
Both	18 (36)	12 (24)	
Blood sugars			
FBS (mg/dl)	234.40±100.64	265.5±102.67	0.128
PPBS (mg/dl)	294.60±105.40	343.18±112.83	0.028

The Group 1 had 46%, 30% and 4% participants with UTSA wound class1B, 2B and 3B, respectively. The Group 2 had 8%, 42% and 24% participants with UTSA wound class 1B, 2B and 3B, respectively. It was found that there was a significant difference in the distribution of wounds according to UTSA classification in both the groups. The group of participants with SIRS (Group 2) had more number of patients with the deeper wounds (2B, 3B), which association between the presence of SIRS and deeper wounds (Table 3).

Table 3: Wound status of the participants of both the groups using UTSA classification.

Wound class	Group 1 No SIRS N (%)	Group 2 SIRS N (%)
0B	1 (2)	0 (0)
1B	23 (46)	4 (8)
1D	2 (4)	0 (0)
2B	15 (30)	26 (52)
2C	1 (2)	0 (0)
2D	6 (12)	7 (14)
3B	2 (4)	12 (24)
3D	0 (0)	1 (2)

Among the participants of the Group 1 and the Group 2, 12 (24%) and 32 (64%) underwent major amputation, respectively. This difference in the number of participants undergoing major amputation from both the groups was statistically significant ($p<0.001$) [(RR 2.66 (95% CI, 1.56-4.55)]. Excluding participants who underwent major amputation remaining participants of both the groups

were compared for minor amputation. From Group 1, 15 (30%) and from Group 2, 10 (20%) participants underwent minor amputations, this difference was not statistically significant (p=0.258). The median of duration of hospital stay was 8.00 days in the participants of the 'Group 1' and 17.50 days in the participants of the 'Group 2'. The duration of the hospital stay was 9.5 days prolonged in the participants of the 'Group 2'. This difference was statistically significant (p<0.001). Also, the duration of ICU stay was significantly prolonged among the participants with SIRS (<0.001) (Table 4).

Table 4: Comparison of the outcome variables.

Outcome	Group 1 (No SIRS)	Group 2 (SIRS)	P value
Major amputation, N (%)	12 (24)	32 (64)	<0.001
Minor amputation, N (%)	15 (30)	10 (20)	0.258
Hospital stay (days), [median (IQR)]	8.00 (4.00-20.50)	17.50 (10.75-38.25)	<0.001
ICU stay (days), [median (IQR)]	0.00 (0.00-0.00)	1.00 (0.00-2.00)	<0.001
Mortality, N (%)	1 (2%)	6 (12%)	0.112*

Association between the number of SIRS criteria present and patients undergoing major amputation was studied. When zero, one, two, three, four and five criteria were present 10%, 33%, 50%, 72% and 80% of them, respectively, underwent major amputation (Figure 1).

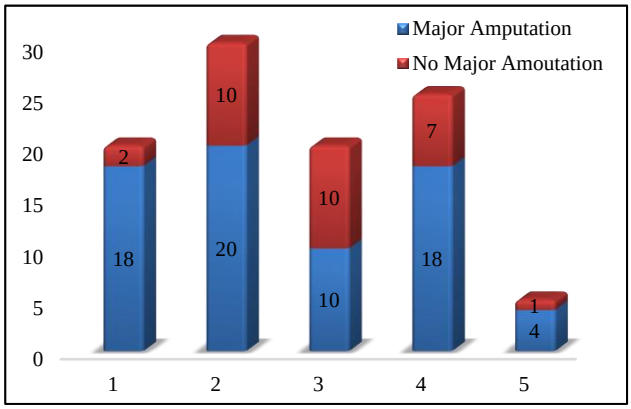

Figure 1: The proportion of patients undergoing major amputation compared to the number of SIRS criteria present.

Out of 55 participants who had mono-microbial infection 18 (32.73%) underwent major amputation and out of 45 participants who had poly-microbial infection 26 (57.87%) underwent major amputation. This difference was statistically significant (p=0.012) (Table 5).

Table 5: Comparison of participants with mono-microbial infection and poly-microbial infection requiring major amputation.

Management	Mono-microbial N (%)	Poly-microbial N (%)	P value
Requiring major amputation	18 (32.73)	26 (57.78)	0.012

From the study population of 100, seven patients succumbed to their illness. Non-statistically significant trend was observed towards mortality among the patients who presented with SIRS (12% versus 2%), which was limited by the smaller number size of the population studied. This might achieve statistical significance when studied for the larger population. Out of these seven, four patients were male and three patients were female. Six patients out of seven who expired during the hospital stay were having SIRS. Three patients were having limb ischemia and four of them had polymicrobial infection. Six out of seven underwent major amputation. None of them underwent minor amputation. Six out of seven patients expired in the post-operative period after major amputation because of sepsis leading to MODS. One patient from the 'Group 1' had myocardial infarction and died because of it.

DISCUSSION

This study observed, 2.66-fold higher risk of major amputation, prolonged duration of hospital and ICU stay among the patients of DFI who presented with SIRS compared to who were not having SIRS at presentation. Presence of polymicrobial infection also had a statistically significant association with the incidence of major amputation. More patients underwent major amputation with the increasing number of SIRS criteria.

Wuckich et al, in there retrospective study reported 7.12-fold higher risk for major amputation in patients having severe DFI (SIRS present) compared to the patients having moderate DFI (SIRS absent), with ~9.5 days longer duration of hospital stay in the participants who were having SIRS at the time of admission.[5] In their study, 37% patients with severe DFI (SIRS present) underwent minor amputation compared to 35% patients having moderate DFI (SIRS absent), this difference could not reach statistical significance.

In the retrospective analysis of 2230 patients with diabetes and skin or soft tissue infection presented to 92

hospitals between January 2003 and June 2007, Lipsky et al, after multivariate analysis reported, temperature <96° F or >100.5° F and white blood cell count >11000/mm^3 to be one of the risk factors for the lower extremity amputation. In the model, they derived to predict the risk of lower extremity amputation, allotted risk score of 2 and 7 to temperature <96° F or >100.5° F and white blood cell count >11000/mm^3, respectively.[8] These two factors roughly correspond to the two criteria required for the diagnosis of SIRS.

In the present study, the duration of the hospital stay among the participants with SIRS and without SIRS was 17.50 (10.75-38.25) days and 8.00 (4.00-20.50) days, respectively, compared to 11.39 (SD, 8.67) days and 7.82 (SD, 6.55) days reported by Wukich et al.[5] In the present study, each unit managing patient had their own policy of discharging diabetic foot infection patients. Most of the patients were discharged after achieving definitive coverage of wound by split skin grafting. The duration which required to make wound fit for grafting and the duration required for the take of the graft was also included in the total duration of the hospital stay. This might be the reason behind the longer duration of hospital stay in the present study compared to the study conducted by Wukich et al.[5]

The participants of this study who had limb ischemia were 41%, which was closer to 43% and 36.2% in the retrospective studies conducted by Wukich et al and Lipsky et al respectively.[5,8] In this study, there was no statistically significant difference in presence limb ischemia among the participants of both the groups, suggesting the presence of SIRS was not associated with limb ischemia. Wukich et al in their retrospective study where they have divided patients into moderate and severe diabetic foot infection using SIRS as the criteria reported no statistically significant difference in the presence of peripheral arterial disease (48% versus 41%; p=0.447) between the participants of both the groups. Also, the number of patients who required vascular surgery were not significantly different between the two groups (9% versus 17%; p=0.22).[5] In one more study conducted by the same authors where they used two or more objective signs of systemic toxicity to differentiate between moderate and severe diabetic foot infection reported no significant difference in the prevalence of peripheral arterial disease among both the groups.[9]

Presence of peripheral arterial disease is a known risk factor for lower extremity amputation. This had been proved in the meta-analysis conducted by Shin et al, which showed a significant association between the presence of peripheral arterial disease and major amputation in the patients with diabetic foot infection (p=0.045).[10] Lipsky et al also reported a significant association between the history of the peripheral vascular disease and lower extremity amputation (p<0.001) [(RR=2.11) (95% CI, 1.66-2.69)].[8] In the present study, the statistically non-significant trend among the participants having limb ischemia for major amputation was found (53.7% versus 37.3%).

Hence, the presence of peripheral arterial disease is an independent risk factor for lower extremity amputation in diabetic foot infection patients. As there is no association between the presence of SIRS and limb ischemia, diabetic foot infection patients should be evaluated for the presence of peripheral vascular disease separately to predict the probability that patient will require any major amputation. Preliminary assessment of which can be done by simple bedside test like ABPI, before subjecting patients for further radiological assessments.

As we were aiming to find simplified objective clinical criteria to classify DFI and predict the outcomes of it, we used SIRS as criteria to classify DFI patients and refrained ourselves from using multiple laboratory-based tests and cumbersome scoring systems. Use of laboratory-based tests is time-consuming and availability of them at the primary health care level is doubtful. SIRS as criteria to classify DFI patient is simple enough to be used by any healthcare worker, regardless of the level in healthcare system he/she is working.

Limitations

This study also had some limitations. As it was conducted in the tertiary care center and South India's apex healthcare institute, it was biased toward recruiting more critically ill patients in the study. Each unit of the department of surgery managed their patients according to their unit policy. No uniform algorithm for management and discharge was used. Patients included in the study were not followed after discharge or after being referred back to a local healthcare facility for further management. Presence or absence of SIRS was recorded only at the time of admission. As the DFI is not a static condition, patient's clinical condition or wound status can deteriorate after admission, and the patient can develop SIRS during the hospital stay, this was not recorded in this study. Even though it would have been considered, the association between SIRS and major amputation is proved in this study, shifting patients from no SIRS group to SIRS group if they develop SIRS during the hospital stay would have decreased proportion of patients undergoing major amputation among patients without SIRS, this would have led to further consolidation of the results.

In the present prospective study, presence of significant association between SIRS and major amputation, prolong duration of hospital stay and ICU stay has been proved. So that, it can be used to predict the outcome of diabetic foot infection patient and also to classify them. Classification of this kind will be clinically relevant, too. This will help in making decision about patients who will require in hospital care and referral to tertiary care centre.

Limited resources which are available with healthcare system can be focused on such patients to achieve better outcomes.

CONCLUSION

Presence of SIRS in patients with DFI is associated with the requirement of major amputation, prolonged duration of the hospital and ICU stay. Hence, the presence SIRS can be predictor of poorer outcome in DFI patient. SIRS can be used to differentiate severe DFI from moderate DFI. Applicability of the same can be tested in the multicenter study, involving the primary health centers and including larger study population.

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