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RESEARCH REPORTS

Factors Affecting Diabetic Foot Ulcer Among Patients Presenting to Wound Care Clinics Across the Maldives.

IBRAHIM AHMED[1], AHMED MAHIL MUAZ[1], AISHATH THOOBA SHAKEEL[1], AHMED DANISH SHAMEEM[1], SUMAA ADAM[1], & BHARAT MANI BANJADE[2]

School of Medicine, The Maldives National University, Male', Maldives.
Department of Surgery, Indira Gandhi Memorial Hospital, Male', Maldives.

ABSTRACT *Diabetic Foot Ulcer (DFU), with an estimated lifetime risk of 25% in diabetic patients, is one of the most disastrous complications of diabetes due to its protracted course of illness and susceptibility to infections. This study aims to assess the factors associated with DFU among adult patients attending to Wound Care Clinics across the Maldives. This hospital-based, case-control study included 61 patients with DFU presented to five government hospitals across the Maldives between April 2023 and April 2024. The control group comprised of 61 diabetic patients without DFU, matched to cases by age group and sex in a 1:1 ratio. Patient demographics and data on all variables considered in the study were collected directly from patients and their hospital clinical records. Chi-square tests were used to assess the association between the variables and DFU. Significant variables were further analyzed using Logistic Regression Models in IBM® SPSS® version 23. The results show that there was an increased likelihood of DFU in patients with an HbA1c level more than 7.5% [OR=2.42, p=0.019, 95% CI: 1.159 – 5.036], on insulin therapy [OR=4.65, p<0.001, 95% CI: 2.101 – 10.288], on Oral Hypoglycemic Agent (OHA) & insulin combination therapy [OR=4.33, p=0.001, 95% CI: 1.860 – 10.068], medication non-compliance [OR=13.2, p<0.001, 95% CI: 4.929– 35.351], Loss of Protective Sensation (LOPS) [OR=27.1, p<0.001, 95% CI: 6.197 – 366.358], Diabetic Neuropathy [OR=27.1, p=0.002, 95% CI: 3.497 – 210.670], and chronic kidney disease [OR=3.0, p=0.019, 95% CI: 1.194 – 7.520]. The risk factors associated with DFU include HbA1c > 7.5%, insulin therapy, insulin and OHA combination therapy, non-compliance to diabetic medications, LOPS, diabetic neuropathy, and CKD. Highest risk of DFU is associated with loss of protective sensation, diabetic neuropathy, and Non-compliance to diabetic medications. Therefore, early interventions to achieve optimal glycemic control and routine screening for diabetic complications must be prioritized to reduce the risk of DFU. Additionally, strategies to improve medication compliance should be integrated into clinical care settings.*

Keywords: Diabetic Foot Ulcer, Risk Factors, Wound Care Clinics, Hospital, Maldives.

Introduction

Diabetic foot ulcer (DFU), defined as a discontinuity of the epidermis and part of the dermis of the foot in an individual with underlying diabetes mellitus is one the many complications associated with diabetes (Atlaw et al., 2022; Goh et al.,

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2020; Guo et al., 2022; Jain & Barman, 2017; Jouhar et al., 2019; Kadhim & Mohammed, 2021; Z. A. Khan et al., 2019; Tolossa et al., 2020; Van Netten et al., 2023; Xie et al., 2017). Literature reveals a global DFU prevalence of 6.3%, with a 5.5% prevalence in Asia and even higher across the countries in isolation (Zhang et al., 2017). Its prevalence is in an increasing trend due to the continuing global rise in the incidence of diabetes (Albalawi et al., 2023).

Multiple studies have demonstrated certain factors that contribute to the development DFU in diabetic patients. The most commonly encountered factors include occupation, smoking, duration of diabetes, glycemic control, insulin therapy, medication compliance, hypertension (HTN), hyper/dyslipidemia, chronic heart disease, peripheral arterial disease (PAD), chronic kidney disease (CKD), diabetic neuropathy (DN), and loss of protective sensation (LOPS) (Akkus & Sert, 2022; Akyüz et al., 2023; Aliyu et al., 2023; Din et al., 2023; Ghanbari et al., 2023; McDermott et al., 2023; Piran et al., 2024; Sarinnapakorn et al., 2016; Syauta et al., 2021; J. Wang et al., 2022; X. Wang et al., 2022; Yazdanpanah et al., 2018).

To date, limited information is available on DFU and their associated factors in the Maldives. This study aims to assess the association of aforementioned factors with DFU among adult patients presenting to Wound Care Clinics across the Maldives. Additionally, a secondary objective, is to characterize the microbiologic profile and antibiotic sensitivity patterns of infected DFU cases within the study sample.

Methods

Study design, setting, and period

This is a hospital-based, matched case-control study carried out in wound clinics, dressing and procedure rooms, and inpatient units of five government hospitals across the Maldives. The study period spanned from April 2023 and April 2024.

Study participants, Sample size, and sampling technique

All patients with diabetes presenting to the data collection hospitals of the study were the source population. Diabetes was defined as having either International Classification of Diseases, Tenth Revision (ICD-10) code E10 Type 1 diabetes mellitus or E11 Type 2 diabetes mellitus. All patients above 18 years of age with a diagnosis of DFU were selected as the case subjects whereas the control subjects were diabetic patients above 18 years of age who have not had a diagnosis of foot ulcer due to any causes during the study period. A manual review of the patient's diagnosis was carried out and a total of 61 DFU patients were identified after excluding patients with ulcers due trauma in road traffic accidents, fracture, gout, thrombosis or venous stasis (Van Netten et al., 2023). We designed the study to have a 1:1 matching to cases in respect to age group and sex. A stratified random sampling technique was employed to select 1 control for each case included in the study. A total sample size of 122 (61 cases and 61 controls) was used in this study.

Data collection tools and procedures

A structured questionnaire based on literature was created to collect data. Interviewer-administered questionnaire technique and a thorough review of the medical records were carried out to collect data from both cases and controls.

Quality assurance, data management and analysis

The original English version of the questionnaire was translated in to Dhivehi language, the official language of the Maldives, with the assistance of linguistic experts. It was then translated back in to English by another person to ensure consistency with the original version. The Dhivehi translate of the questionnaire was used to collect data.

A pilot study was conducted on 8% (n=10) of the study sample size in Indira Gandhi Memorial Hospital, Male, Maldives. Ambiguous components of the questionnaire were changed accordingly.

Five researchers collected the data from cases and controls in the actual study. The supervisor supervised the overall data collection process. All collected data was stored in password encrypted files and all collected data will be erased within six months of publication. The data were processed using IBM® SPSS® version 23 and Microsoft Excel 2021 after checking for its completeness.

Descriptive statistics were run to describe the characteristics of the study sample in relation to relevant variables (sex, age group, occupation, comorbidities, treatment therapies, medication compliance, and glycemic control). These were expressed as frequency percentages and means ± standard deviation (SD). Chi-square (x^2) tests were used to assess the association between the potential risk factors included in the study and DFU. Variables with a x^2 value less than 0.05 were then further analyzed using bivariate Logistic Regressions Models. The magnitude of the associations was measured using Odds Ratio (OR) with 95% confidence interval. The fitness of the model was evaluated using Hosmer-Lemeshow goodness-of-fit. The statistical significance for the study was set at $p<0.05$.

Results

A total of 61 cases and 61 controls were recruited for the study, with the descriptive data on their demographics and personal characteristics presented in Table 1. Among both cases and controls, 52% (n=32) were male, and 48% (n=29) were female, as the participants were matched for age and sex in a 1:1 ratio.

The age distribution of participants in both groups were identical. The mean age of the cases and their matched controls was 61.48 ± 1.17 years. The smallest number of participants fell into the two extremes of the age groups, 5% (n=3) were under 40 years, and 7% (n=4) were above 80 years. Half of the participants were in ages between 61 years and 80 years, i.e., 25% (n=15) the 61-70 age group and 25% (n=15) in the 71-80 age group.

A large proportion of participants in the case group was either unemployed (48%, n=29) or retired (26%, n=16). Similarly, in the control group, 25% (n=15) of the participants were unemployed and 39% (n=24) were retired. Only 26% (n=16) of the participants in the case group were gainfully employed while this amount was at 36% (n=22) for the control group. The number of smokers were generally low in both cases (28%, n=17) and control group (23%, n=14).

Table 2 presents the descriptive data on clinical factors of the study sample. All participants in both cases and control group had Type 2 diabetes mellitus. The mean duration of diabetes among the cases was 14.8 ± 1.7 years while the controls had a mean duration of 10.7 ± 1.1 years. Our results show that insulin usage was high among the cases (56%, n=34) while this was comparatively lower among the

controls (21%, n=13). Additionally, 46% (n=28) of the participants in the case group were on insulin and oral hypoglycemic agents (OHA) combination therapy. This number was lower among the participants in control group (16%, n=10). Compliance to diabetic medications was poor among the case group (59%, n=36) while the majority of the patients in control group (90%, n=55) were compliant to their diabetic medications. The glycemic control was also poor among the participants in the case group with a little more than half of the participants having an HbA1c level above 7.5% (54%, n=33) while 33% (n=20) of the participants in the control group had an HbA1c level above 7.5%. The mean HbA1c was at 8.4 ± 0.34% in the case group and at 7.3 ± 0.18% in the control group.

The prevalence of comorbidities in both cases and controls shows that among the control group only 2% (n=1) were diagnosed with diabetic neuropathy while 66% (n=40) has HTN and no participants had PAD. Further, 82% (n=50), 13% (n=8), and 16% (n=10) were diagnosed with hyper/dyslipidemia, CKD, and chronic heart disease respectively. Diabetic neuropathy was a more common finding in the case group as 31% (n=19) of the group were diagnosed with diabetic neuropathy, while 57% (n=35) were diagnosed with HTN. Further, 30% (n=18) were diagnosed with PAD making it more prevalent among the case group. 80% (n=49) were diagnosed with hyper/dyslipidemia. Additionally, 31% (n=19), and 21% (n=13) were diagnosed with CKD, and chronic heart disease respectively.

A swab from the ulcer was sent for culture and sensitivity testing in 44% (n=27) of the total cases included in the study. At least one type of bacteria was isolated in 81% (n=22) of the swabs sent for culture and sensitivity testing while 19% (n=5) showed no growth. More than 1 type of bacteria were isolated in 7% (n=2) of the swab samples summing the number of individual isolates to 24 of which 42% (n=10) of isolates were Gram positive while 58% (n=14) were Gram negative isolates.

The most frequently isolated single etiological agent was Staphylococcus aureus which was isolated in 33% (n=8) of the swab samples. Notably, 75% (n=6) of Staphylococcus aureus strains isolated in our study were resistant to Benzylpenicillin while all (100%, n=8) the strains were found to be sensitive to Oxacillin and Trimethoprim/Sulfamethoxazole. Other frequently encountered sensitive antibiotics include Gentamycin (sensitive: 88%, n=7; resistant: 12%, n=1), Ciprofloxacin (sensitive: 88%, n=7; resistant: 12%, n=1), and Erythromycin (sensitive: 50%, n=4; intermediate: 12.5%, n=1; resistant: 37.5%, n=3).

The second most commonly isolated agent was Klebsiella pneumoniae (21%, n=5). The frequently encountered sensitive antibiotics include Amikacin (sensitive: 80%, n=4; resistant: 20%, n=1), Piperacillin/Tazobactam (sensitive: 80%, n=4; resistant: 20%, n=1), Gentamycin (sensitive: 60%, n=3; intermediate resistance: 20%, n=1; resistant: 20%, n=1), and Ciprofloxacin (sensitive: 60%, n=3; resistant: 40%, n=2).

Pseudomonas aeruginosa (21%, n=5) was the third most common isolate. The frequently encountered sensitive antibiotics include Cefepime (sensitive: 100%, n=4), Piperacillin/Tazobactam (sensitive: 100%, n=4), Amikacin (sensitive: 75%, n=3; resistant: 15%, n=1), and Ciprofloxacin (sensitive: 75%, n=3; resistant: 15%, n=1).

Table 1
Demographic and Personal Characteristics of the Study Sample

Variables	DFU % (n) n=61	No DFU % (n) n=61
Sex		
Male	52% (32)	52% (32)
Female	48% (29)	48% (29)
Age Groups		
<40 years	05% (03)	05% (03)
41-50 years	21% (13)	21% (13)
51-60 years	18% (11)	18% (11)
61-70 years	25% (15)	25% (15)
71-80 years	25% (15)	25% (15)
>80 years	07% (04)	07% (04)
Mean age ± SD	61.48 ± 1.17 years	
Occupation		
Field/site jobs	13% (08)	20% (12)
Administrative jobs	13% (08)	16% (10)
Retired	26% (16)	39% (24)
Unemployed	48% (29)	25% (15)
Cigarette smoking		
Smoker	28% (17)	23% (14)
Non-smoker	72% (44)	77% (47)

Table 2
Clinical Factors of the Study Sample

Variables	DFU % (n) n=61	No DFU % (n) n=61
Type of diabetes		
Type 1 Diabetes Mellitus	0% (0)	0% (0)
Type 2 Diabetes Mellitus	100% (61)	100% (61)
Duration of diabetes		
Less than 10 years	51% (31)	41% (67)
More than 10 years	49% (30)	33% (20)
Mean duration of diabetes ± SD	14.8 ± 1.7	10.7 ± 1.1
Treatment therapy		
On insulin	56% (34)	21% (13)
Not on insulin	44% (27)	79% (48)
On Insulin & OHA combination	46% (28)	16% (10)
Not on Insulin & OHA combination	54% (33)	84% (51)
Compliance to diabetic medications		
Compliant	41% (25)	90% (55)

Not compliant	59% (36)	10% (06)
HbA1c		
<7.5%	46% (28)	67% (41)
>7.5%	54% (33)	33% (20)
Mean HbA1c ± SD	8.4 ± 0.34	7.3 ± 0.18
Comorbidities		
Diabetic neuropathy		
Present	31% (19)	2% (1)
Absent	69% (42)	98% (60)
PAD		
Present	30% (18)	0% (0)
Absent	70% (43)	100% (61)
CKD		
Present	31% (19)	13% (8)
Absent	69% (42)	87% (53)
HTN		
Present	57% (35)	66% (40)
Absent	43% (26)	34% (21)
Hyper/dyslipidemia		
Present	80% (49)	82% (50)
Absent	20% (12)	18% (11)
Chronic Heart Disease		
Present	21% (13)	16% (10)
Absent	79% (48)	84% (51)
Loss of protective sensation (LOPS)		
Intact	56% (34)	98% (60)
Lost	44% (27)	02% (01)

Chi-square test of independence was performed to assess the association between the variables and DFU. The results are tabulated in Table 3. A significant association with DFU was found in diabetic neuropathy [x^2 (1, N = 122) = 19.4, p < .01], CKD [x^2 (1, N = 122) = 5.8, p = .016], LOPS [x^2 (1, N = 122) = 31.2, p < .01], glycemic control (HbA1c level) [x^2 (1, N = 122) = 5.6, p = .018], insulin therapy [x^2 (1, N = 122) = 15.3, p < .01], OHA & insulin combination therapy [x^2 (1, N = 122) = 12.4, p < .01], and compliance to diabetic medications [x^2 (1, N = 122) = 32.7, p < .01].

No significant association was found in occupation [x^2 (4, N = 122) = 7.9, p = .095], smoking [x^2 (1, N = 122) = 0.4, p = .533], duration of diabetes [x^2 (1, N = 122) = 3.4, p = .066], HTN [x^2 (1, N = 122) = 0.9, p = .35], hyper/dyslipidemia [x^2 (1, N = 122) = 0.05, p = .817], chronic heart disease [x^2 (1, N = 122) = 0.5, p = .487], and PAD [x^2 (1, N = 122) = 21.1, p = .19].

Table 3
Pearson's chi-squared test results

Variable	p-value for $\chi 2$
Occupation	0.095
Smoking	0.533
Duration of Diabetes	0.066
HbA1c Level	0.018*
Insulin Therapy	<0.001*
Insulin & OHA combination	<0.001*
Compliance to diabetic medications	<0.001*
HTN	0.350
Hyper/dyslipidemia	0.817
Chronic Heart Disease	0.487
PAD	0.190
Diabetic Neuropathy	<0.001*
CKD	0.016*
LOPS	<0.001*

** $\chi 2$ test, significant with the p-value <0.05*

Table 4
Logistic regression model to assess the impact of variables on DFU

Variable	Odds Ratio	95% Confidence interval	p-value*
Glycemic control			
HbA1c < 7.5%	Ref	-	-
HbA1c > 7.5%	2.42	1.159 - 5.036	0.019
Insulin therapy			
Yes	4.65	2.101 - 10.288	<0.001
No	Ref	-	-
Insulin & OHA combination			
Yes	4.33	1.860 - 10.068	0.001
No	Ref	-	-
C***ompliance to diabetic medications***			
Compliant	Ref	-	-
Non-compliant	13.2	4.929 - 35.351	<0.001
LOPS			
No LOPS	Ref	-	-
LOPS	47.6	6.197 - 366.358	<0.001
Diabetic Neuropathy			
Present	27.1	3.497 - 210.670	0.002
Absent	Ref	-	-

CKD			
Present	3.0	1.194 - 7.520	0.019
Absent	Ref	-	-

* *p-value significant <0.05*

The risk factors of DFU which were significant at p-value<0.05 were HbA1c > %7.5 [OR=2.42, p=%95 ,0.019 CI: 5.036 – 1.159], insulin therapy [OR=4.65, p<%95 ,0.001 CI: 10.288 – 2.101], insulin and OHA combination therapy [OR=4.33, p=%95 ,0.001 CI: 10.068 – 1.860], non-compliance to diabetic medications [OR=13.2, p<%95 ,0.001 CI: 35.351 –4.929], LOPS [OR=27.1, p<%95 ,0.001 CI: 366.358 – 6.197], diabetic neuropathy [OR=27.1, p=,0.002 %95 CI: 210.670 – 3.497], and CKD [OR=3.0, p=%95 ,0.019 CI: 7.520 – 1.194] as shown in Table 4.

Results

The duration of diabetes and PAD were highlighted by several authors as important risk factors that contribute to development of DFU (Aliyu et al., 2023; Al-Rubeaan et al., 2015; Fauzi et al., 2016; McDermott et al., 2023; Piran et al., 2024; Syauta et al., 2021; Woldemariam et al., 2020). Although our study did not find a statistically significant association of duration of diabetes with DFU, it could still be a potential risk factor in our setting, since the mean duration of diabetes was 14.8 ± 1.7 years among the participants in the case group. Studies have shown that having diabetes for more than 10 years was associated with an increased risk of DFU (Al-Rubeaan et al., 2015; Mohammed et al., 2016; Piran et al., 2024; Syauta et al., 2021). The variation observed in PAD might be because it is likely underdiagnosed due to diagnostic challenges (McDermott et al., 2023).

In this study, participants who had an HbA1c level > 7.5% were 2.42 times more likely to develop a DFU compared to participants who had an HbA1c level < 7.5%. This finding is consistent with the findings of other recent studies, such as those conducted by Ghanbari et al. (2023) who reported that a 2% increase in HbA1c level increases the risk of DFU by 1.6 times. In addition, J. Wang et al. (2022) in their study on Prediction for the Risk of Diabetic Foot found a strong association between elevated HbA1c levels and the risk of developing DFU. The study also identified HbA1c is an independent risk factor for the development of DFU. Zhang et al. (2017) have also reported the same in their metanalysis. Another study by X. Wang et al. (2022) found intensive glycemic control in patients with diabetes to delay the occurrence of complications such as peripheral neuropathy, and nephropathy, both of which are main risk factors for DFU.

Our findings show that participants who were on insulin therapy were 4.65 times more likely to develop DFU than those who were not on insulin therapy. Similarly, a 4.33 times increased likelihood of developing DFU was observed among participants who were on insulin and OHA combination therapy compared to who were not on combination therapy. These findings are compatible with a previous study on incidence and risk factors of DFU by Yazdanpanah et al. (2018), who reported the odds of DFU in patients using insulin to be 5.78 times greater. Similar findings were also reported by Al-Rubeaan et al. (2015); M. I. H. Khan et al. (2018); Mohammed et al. (2016); Woldemariam et al. (2020). Another recent

study by Piran et al. (2024) and Fauzi et al. (2016) found insulin therapy to be significantly associated with increase in occurrence of diabetic foot ulcer. This could be explained based on Ghanbari et al. (2023)'s finding that insulin usage is associated with an elevated HbA1c level. Insulin and OHA combination therapy were also found to be linked with an increased risk of development of DFU (M. I. H. Khan et al., 2018; Mohammed et al., 2016). These treatment therapies reflect uncontrolled glycemic levels as insulin is usually started when the target HbA1c levels for optimal glycemic control is not achieved with the initial OHA therapy alone (American Diabetes Association Professional Practice Committee, 2024).

This study also shows that non-compliance to diabetic medications increase the risk of DFU by 13.2 times compared to those who were compliant to their diabetic medications. The finding is consistent with findings of M. I. H. Khan et al. (2018) and Mohammed et al. (2016) who reported poor compliance to treatment therapies to be associated with an increased risk of DFU. This could be explained, as non-compliance would eventually lead to elevated HbA1c, which is an independent risk factor for the development of DFU as discussed previously (M. I. H. Khan et al., 2018; J. Wang et al., 2022).

In this study, patients with diabetes who have diabetic neuropathy were 27.1 times more at risk to develop DFU than patients with diabetes without diabetic neuropathy. Additionally, LOPS was found to increase the risk of DFU by 47.6 times compared to those did not have LOPS. These findings are consistent with that of other authors such as Yazdanpanah et al. (2018) who found that DFU was 3.51 times more likely in patients who had neuropathy. Moreover, Woldemariam et al. (2020) have also reported a similar finding. Adding weightage to this, J. Wang et al. (2022) in their study on risk factors of DFU found that neuropathy is responsible for 16%-66% of the cases of diabetic foot syndrome. LOPS, like diabetic neuropathy increases the likelihood of minor injuries going unnoticed due to the decline in sensation of pain in the foot. This leads to the development of pre-ulcerative lesions or minor wounds that persist unnoticed, potentially delaying their diagnosis (Aliyu et al., 2023; Piran et al., 2024; J. Wang et al., 2022; Yazdanpanah et al., 2018).

The current study showed that 31% of patients who presented with DFU were diagnosed with CKD. In agreement with our findings, Usman (2020) reported that nearly one third (31%) of type 2 diabetes mellitus patients who had a foot ulcer had a concomitant kidney disease. A meta-analysis carried out by Jin & Xu (2024) states that individuals with nephropathy have low Hb levels and poor peripheral vascular status which obstructs tissue perfusion resulting in worsening of limb ischemia and delayed wound healing. Supporting this statement, their study showed individuals with DFU had a higher risk of renal failure, higher serum creatinine and low estimated glomerular filtration rate (eGFR) compared to non-DFU patients. Other authors have reported similar association between occurrence of DFU and decrease in eGFR, a key indicator of renal function as well as the stage of CKD (Bonnet & Sultan, 2022; Dugbartey & Alornyo, 2022). Further, Dugbartey & Alornyo (2022) found that the risk of developing diabetic foot ulcers increased by twofold and threefold in patients with CKD stage 3 and 4 respectively.

Our findings show that the most frequently isolated single etiological agent from swab cultures of DFU cases presenting with features of infection was Staphylococcus aureus. This result is concurrent with findings from Aleem et al. (2021); Atlaw et al. (2022); Du et al. (2022); Jain & Barman, (2017); Shahrokh et al. (2022) which also demonstrated Staphylococcus aureus predominance. Notably, majority of Staphylococcus aureus strains isolated in our study were resistant to

Benzylpenicillin while all the strains were found to be sensitive to Oxacillin, a penicillinase-resistant penicillin, and Trimethoprim/Sulfamethoxazole. This was in contrast to Aleem et al. (2021); Dogan (2018); Jain & Barman (2017); Z. A. Khan et al. (2019) in which the vast majority of Staphylococcus aureus isolates demonstrated resistance to methicillin, which is an antibiotic in the same class as oxacillin. However, similar findings as this study were reported by most of the aforementioned authors with regards to the prevalence of Klebsiella pneumoniae and Pseudomonas among the Gram-negative isolates.

Conclusion

The primary objective of this study was to assess the factors that are associated with DFU among adult patients presenting to Wound Care Clinics across the Maldives. The identified risk factors were HbA1c > 7.5%, insulin therapy, insulin and OHA combination therapy, non-compliance to diabetic medications, LOPS, diabetic neuropathy, and CKD. Hence, early interventions to achieve optimal glycemic control and screening for diabetic complications must be emphasized to reduce the risk of DFU. Additionally, methods to improve medication compliance must be encompassed within clinical settings.

Limitations

Our study has certain limitations including small sample size. However, for this reason, we have used a matched case-control study design. Moreover, non-parametric tests were employed in the study and effect size has been declared wherever required. Additionally, further studies in-cooperating potential risk factors with larger sample size and for a longer study period is recommended. Another limitation to our study is that a greater proportion of participants were from one hospital, IGMH, which could introduce selection bias. However, as stated previously, IGMH serves as the referral center and focal point of the Maldives, resulting in a greater variation among the study sample.

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