Epidemiology and Outcome of MRSA Infection in Governmental Health Care Facilities in Bahrain

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Objective: MRSA is an important human pathogen causing wide-ranging spectrum of clinical presentation, there is no previous details about the epidemiology of MRSA in Bahrain. This study aims to ascertain MRSA prevalence at the governmental health care facilities & describe its epidemiology; to be used as a benchmark for the prevalence of MRSA in Bahrain & direct future studies.

Design: retrospective study

Setting: SMC Microbiology laboratory covering all governmental health care facilities

Method: Analysis of all MRSA isolates during 2019

Results: Total of 566 MRSA isolates were identified, prevalence of MRSA in our study 22% of all Staphylococcus aureus isolates. Male gender contributes to higher proportion of the cases (60%). The most common clinical samples were pus (63%) followed by blood (12%) and respiratory specimens (9%). Out of the total 566 MRSA isolates; 297 (52%) were obtained from outpatients and 269 (48%) were obtained from inpatients. Among the 269 inpatients: 98 isolates (36%) were HO, while 171 isolates (64%) were CO. Mortality among inpatients with MRSA was 10.4%, significantly predominant among HO isolates (23.5 % for HO & 2.9 among CO, p value < 0.001), 96% of mortality cases was among inpatients with blood & respiratory isolates.

Conclusion: In our study, prevalence of MRSA was on the lower limit compared to worldwide rate, but majority of our MRSA was of community onset which enthuse further focused studies on CO MRSA to delineate its risk factors at community level.

INTRODUCTION

Staphylococcus aureus is an important cause of human disease, it was initially isolated from a surgical abscess in 1880 and described as an important pathogen in localized skin and soft tissue infection[1]. It is recognized as a cause of a wide-ranging spectrum of clinical presentation, starting from asymptomatic skin colonization passing through minor skin infections, chronic bone infections extending to devastating septicemia and endocarditis with accompanying very high mortality[2].

Important events in the evolution of S. aureus is the development of Methicillin-Resistant Staphylococcus aureus (MRSA) which was described initially in 1961,then shortly after that spread worldwide .The problem with MRSA strain is not only the methicillin resistant; but that the pathogen also commonly harbor genes associated with increased virulence & resistance to many other antibiotics , hence MRSA infection usually is a therapeutic challenge as it leaves the clinician with very few treatment options such as glycopeptides and linezolid[3-5].

MRSA has spread worldwide, and it became now endemic in most part of the world with variable prevalence ranging from 20% in some countries to 50% in others[6-7]. It also shows great variability from an institute to other & among each different clinical location; being highest in critical care units[8].

There are two main types of MRSA, Hospital-Onset (HO-MRSA) and Community-Onset (CO-MRSA) which differ with respect to their clinical, molecular epidemiology and antimicrobial profile, CO-MRSA is usually defined as MRSA infection collected in an outpatient location or an inpatient location less than or equal to 48 hours after admission to the health care facility, while HO-MRSA is defined as MRSA infection that occurs >48 hours following hospitalization[9,10].

For more detailed definition, CO-MRSA is further stratified into Health-care Associated (HA-CO MRSA) and Community Associated (CA-CO MRSA), where HA-CO MRSA is defined as MRSA infection that is acquired outside the hospital setting but patient would have a history of previous exposure to health care system within the past 12 months (eg, history of surgery, hospitalization, dialysis, or residence in a long-term care facility, while CA-CO MRSA lack such exposure history[11].

HA-MRSA strains tend to have multidrug resistance[12] and are usually associated with severe invasive disease, including skin and soft tissue infection, surgical site infection, bloodstream infection, and pneumonia[13-18].

CA-MRSA is most often associated with skin and soft tissue infections in young, otherwise healthy individuals[19]. Most CA-MRSA strains are sensitive to non-beta-lactam antibiotics, but a multidrug-resistant strain has been described with resistant to fluoroquinolones, tetracycline,

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macrolides and clindamycin[20-21].

In this study, we aimed to improve our knowledge of the local epidemiology of MRSA infection in the governmental health care facilities in the kingdom of Bahrain, define the antibiotics sensitivity profile and assess the outcome of patients with MRSA infection.
Up to our knowledge, no previous study has been conducted to describe the epidemiology of MRSA in Bahrain.

Reviewing our local epidemiology and antibiotics profile of MRSA should be of great value to identify & target the high-risk group patients for preventive measures, also it is crucial for guidance of treatment to select the most appropriate empirical antibiotics regimen for MRSA infection once suspected or identified before obtaining the full sensitivity profile of in-vitro testing.

MATERIALS AND METHODS

Setting & Study Population: This study was conducted at Salmaniya Medical Complex (SMC). All patients with MRSA infection during one year period (January 2019-December 2019) were identified from microbiology database system from various clinical specimens received in SMC microbiology lab , which is the main governmental microbiology lab that covered all Ministry of Health (MOH) facilities in Bahrain (both inpatients facilities comprising 1 tertiary care & 4 secondary care centers and outpatients facilities including diverse outpatients clinics in SMC, 2 outpatient main governmental hemodialysis units & 27 primary health centers) . Demographic, epidemiological, and microbiological data was collected from electronic medical records for all included patients.

Design: Retrospective analytical study of all patients with positive MRSA infection (all clinical isolates identified in SMC microbiology lab)

Definition:

Clinical Isolates: The first non-repetitive positive growth of MRSA for each patient from any clinical specimen during the study period was counted as clinical isolate.
All screening samples were excluded. MRSA isolates were considered duplicate & not encountered if it was identified from the same patient with identical antimicrobial profile, Patients with more than one clinical isolates including blood was considered as one blood isolate for the analysis.

Laboratory Technique: These isolates were identified by conventional phenotypic methods such as colony morphology, Gram's stain, catalase test, slide and tube coagulase test, growth on mannitol salt agar, the Bruker MALDI Biotyper (Bruker Daltonics, Billerica, MA) matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS).

Identification of MRSA: All Staphylococcus aureus isolates were subjected to Cefoxitin disc diffusion testing using a 30 µg Cefoxitin disc. The results were interpreted according to CLSI guidelines[22] with an inhibition zone diameter of ≤ 24 mm been reported as Methicillin resistant and ≥ 25 mm as Methicillin sensitive.

Antibiotic Susceptibility Testing: All MRSA isolates were tested for their susceptibility to various antibiotics using BD Phoenix (BD Diagnostics, Baltimore, MD) and interpretation was done according to the Clinical Laboratory Standards Institute (CLSI)[22].

All MRSA isolates (except urine) were tested routinely for the following list of antibiotics: Clindamycin, Erythromycin, Oxacillin, Penicillin, Tetracycline, Tigecycline, Cotrimoxazole and Vancomycin; with addition of Chloramphenicol for eye swab isolates. Urine isolates were tested for the following list of antibiotics: Oxacillin, Penicillin, Cotrimoxazole, Vancomycin, Gentamicin and Nitrofurantion.

Inpatients /Outpatients: Inpatients was defined as patients admitted to the health care facilities (secondary or tertiary care centers), while outpatients included the following categories:
- Patients attending the outpatient clinics in SMC
- Patients attended primary health centers outpatient visit
- Patients attending the emergency department in SMC & discharged without need of admission
- Patients attending the outpatient's hemodialysis unit

Community Onset MRSA (CO MRSA)/ Hospital Onset MRSA (HO MRSA): In reference to WHO & CDC definition[9,10], onset is assigned based on the location of specimen collection (inpatients Vs. outpatients) and date of collection in relation to the admission date for inpatient.

All outpatients were counted as CO. Considering inpatients, those who had collection of clinical samples for microbiology at the time of admission or within the initial 48 hours from admission to the facility was encountered as CO, while those who had the collection of clinical specimens after 48 hours from the admission was counted as HO.

Mortality: This outcome was considered only among impatiens. Death (All-cause mortality) was defined based on the status of the inpatients at the time of discharge from the facility (Alive/Dead)

Data Statistical analysis: Patient baseline characteristics including age, sex, nationality, antimicrobial sensitivity profiles, onset and site of the infections were collected. Statistical analyses were conducted using SPSS 23 software. For categorical measures, frequencies and percentages were computed, while means and standard deviations were calculated for continuous measures. As appropriate, descriptive comparisons were made using $\chi 2$ or Fisher's exact test for categorical variables and t-test for continuous variables. A P-value of less than 0.05 was considered to indicate statistically significant difference.

RESULT

Out of total of 2572 of Staphylococcus aureus isolates identified in SMC microbiology laboratory during the study year; 566 isolates were found to be MRSA, making our prevalence of MRSA 22% of all Staphylococcus aureus isolates.

The age of patients from whom MRSA were obtained ranged from 1 month to 92 years of age, with mean age of 36 years; the biggest proportion of patients were from both age groups 25-34 & 35-44 years as shown in table 1 below. It was noticed that male contribute to higher proportion (337, 60%) of the cases. Bahraini nationality was encountered among 373 patients (66%).

Table 1: Age distribution of Patients with MRSA infection

Age group	Number	Percentage
0-14	96	17%
15-24	50	9%
25-34	116	21%
35-44	119	21%
45-54	77	13%
55-64	50	9%
65 and above	58	10 %
Total	566	100%

Variable clinical samples from which MRSA were isolated are shown in figure 1. The most common clinical samples were pus (63%) followed by blood (12%) and respiratory specimens (9%), followed by ear & eye swab which contribute to 5% & 4%, respectively.

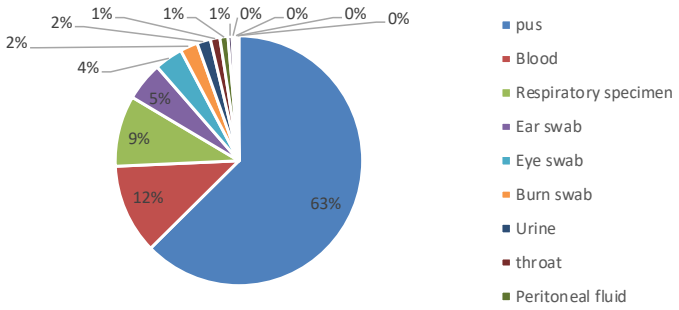

Figure 1: Various clinical samples of MRSA Isolates

Out of the total 566 MRSA isolates identified in SMC microbiology lab; 297 (52%) were obtained from outpatients and 269 (48%) were obtained from inpatients. Among the 269 inpatients: 98 isolates (36%) were HO, while 171 isolates (64%) were CO.
Considering the number of patients admitted to SMC during the study period which was 48827, overall prevalence of MRSA among inpatients in SMC is 47 cases per 10,000 admission.

It was noticed that the majority of MRSA isolates (468, 83% of total) was considered CO (comprising clinical isolates obtained from outpatients' facilities such as SMC clinic, primary health centres and haemodialysis units and among inpatients if specimen collected within 48 hours from admission to the hospital), while only 98 MRSA isolates (17%) were HO (encountered after 48 hours from the time of admission for inpatients). Stratifying the isolates by various clinical samples disclosed that predominance of CO cases was significantly encountered among pus, urine, ear & eye swabs specimens, as shown in table 2 below.

Antibiotics resistance among all MRSA isolates (total & segregated into CO & HO) are shown in figure 2 & table 3. All the isolates were resistance to Oxacillin & Penicillin but retained full sensitivity to Vancomycin & Tigecycline. The percentage of resistance to Cotrimoxazole, Tetracycline, Clindamycin and Erythromycin were found to be 11, 18, 22 & 37%, respectively. Among Eye swab isolates; percentage of resistance to Chloramphenicol was 11%.

When stratifying the data by onset of acquisition into CO & HO, there was no statistically significant difference between the CO & HO isolates with regard the percentage of resistance.

As shown in table 4 below there was variability of resistance pattern among different clinical specimen of MRSA, blood isolates showed 40% resistance to Erythromycin and 26% resistance to Clindamycin with 18% to Cotrimoxazole and 17 % to Tertracycline.

Respiratory isolates showed resistance of 35%, 27%, 13 % &21% to Erythromycin, Clindamycin, Cotrimoxazole and Tertracycline, respectively.

Table2: Distribution of CO & HO among all & various Samples of MRSA isolates

Specimen	Total Patients Number	HO Patients Number (%)	CO Patients Number (%)	P value
Pus specimen	355	24 (6.76%)	331 (93.24%)	<0.001
Blood specimen	66	22 (33.33%)	44 (66.67%)	0.007
Respiratory specimen	52	30 (57.69%)	22 (42.31%)	0.055
Ear swab specimen	28	2 (7.14%)	26 (92.86%)	<0.001
Eye swab specimen	21	5 (23.81%)	16 (76.19%)	<0.001
Burn swab specimen	13	8 (61.54%)	5 (38.46%)	0.230
Urine specimen	10	0 (0%)	10 (100%)	<0.001
Throat swab specimen	7	1 (14.29%)	6 (85.71%)	0.009
Peritoneal fluid specimen	6	2 (33.33%)	4 (66.67%)	0.260
Others*	8	4 (50%)	4 (50%)	0.690
Total	566	98 (17.31%)	468 (82.69%)	<0.001

**Others: Central Line Cath Tip, Cerebral Spinal Fluid, Pleural Fluid, Seminal Fluid, Synovial fluid specimens*

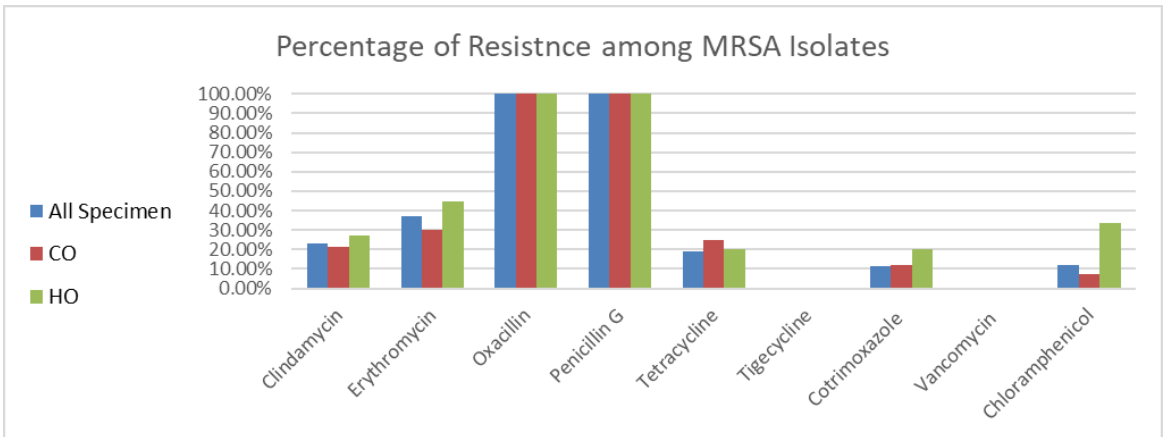

Figure 2: Percentage of resistance among MRSA isolates

Eye swab isolates showed high level of resistance to Erythromycin & Clindamycin (100% & 42%, respectively). Considering the urine specimens, all the identified 10 MRSA isolates were CO, and they were all fully sensitive to the tested antibiotics (Cotrimoxazole, Gentamicin, Nitrofurantion, Vancomycin), but showing minimal resistance of 10% for Norfloxacin.

Mortality among inpatients with MRSA (all-cause mortality) was 28 out of total 269 inpatients (10.4%), stratifying the data into CO & HO groups revealed significant higher mortality among HO isolates (23.5 % for HO & 2.9 among CO, p value < 0.001). 27 out of 28 mortality cases were among inpatients with respiratory and blood specimen (15 &12 patients respectively), while one mortality case was encountered among one inpatient with MRSA pus isolates (case with complicated skin & soft tissue infection), details of mortality data are display below in table 5& 6 below.

DISCUSSION

Worldwide there is considerable variation of MRSA prevalence among all S. aureus isolates ranging between 13% - 74%[23] with last reported data in 2019 as MRSA prevalence of 26.8 % &47 % from Europe & north America, respectively[24].

Aly M. et al reported also a variable rate of MRSA prevalence among clinical isolates from Gulf Corporation Council (GCC) Countries in their metanalysis in 2012[25] where Oman had alarmingly high prevalence of 58% (This result, however, should be considered with caution because their study population was only inpatients in burn unit & all isolates were of hospital onset[26]), while Kuwait was the lowest of 3.3%. Bahrain & Saudi Arabia reported to have 8.5 % & 30 % respectively.

In our current study the prevalence of MRSA during 2019 was 22% among all S. aureus isolates (CO& HO), which fall on the lower limit of

Table 3: Percentage of resistance among MRSA isolates to different antibiotics

Antibiotics	**All Specimen[1] Total Number: 556 Number (%)**	**CO (All) Total number: 458 Number (%)**	**HO (All) Total number: 98 Number (%)**	**P value**
Clindamycin	124 (22.30%)	95 (20.74%)	29 (29.60%)	00.56
Erythromycin	210 (37.80%)	170 (37.12%)	40 (40.81%)	0.493
Oxacillin	556 (100.00%)	458 (100.00%)	98 (100.00%)	N/A*
Penicillin G	556 (100.00%)	458 (100.00%)	98 (100.00%)	N/A*
Tetracycline	105 (18.88%)	88 (19.21%)	17 (17.35%)	0.668
Tigecycline	0 (0.00%)	0 (0.00%)	0 (0.00%)	N/A*
Cotrimoxazole	64 (11.30%)	52 (11.35%)	12 (12.24%)	0.802
Vancomycin	0 (0.00%)	0 (0.00%)	0 (0.00%)	N/A*
Antibiotics	Eye Specimen[2] Total Number: 17 Number (%)	CO Total number: 14 Number (%)	HO Total number: 3 Number (%)	P value
Chloramphenicol	2 (11.76%)	1 (7.14%)	1 (33.33%)	0.331

** NA: Not Applicable*
1: All specimens except urine
2: chloramphenicol susceptibility is done for eye swabs only

Table 4: Percentage of resistance among various samples of MRSA isolates

Specimen	**Clindamycin**	**Erythromycin**	**Oxacillin**	**Penicillin G**	**Tetracycline**	**Tigecycline**	**Trimethoprim/ Sulphamethoxazole**	**Vancomycin**	**chloramphenicol (Eyes only)**
Pus	20.28%	37.75%	100.00%	100.00%	20.85%	0.00%	10.42%	0.00%	
Blood	25.76%	40.91%	100.00%	100.00%	16.67%	0.00%	18.18%	0.00%	
Burn Swab	0.00%	0.00%	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	
Catheter Line Tip	0.00%	0.00%	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	
CSF	0.00%	5.00%	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	
Respiratory	26.92%	34.62%	100.00%	100.00%	21.15%	0.00%	13.46%	0.00%	
Ear Swab	3.57%	31.03%	100.00%	100.00%	7.14%	0.00%	7.14%	0.00%	
Eye Swab	42.86%	100.00%	100.00%	100.00%	19.05%	0.00%	9.52%	0.00%	11.76%
Synovial Fluid	0.00%	0.00%	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	
Peritoneal Fluid	16.67%	16.67%	100.00%	100.00%	16.67%	0.00%	16.67%	0.00%	
Pleural Fluid	0.00%	0.00%	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	
Seminal fluid	0.00%	0.00%	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	
Throat	42.86%	42.86%	100.00%	100.00%	100.00%	0.00%	0.00%	0.00%	

Table 5: Mortality for inpatients with MRSA (CO Vs. HO)

Mortality for All inpatients Total number: 269 Patients Number (%)	Mortality for CO Total number: 171 Patients Number (%)	Mortality for HO Total number: 98 Patients Number (%)	P value
28 (10.41%)	5 (2.92%)	23 (23.47%)	<0.001

Table 6: Mortality for inpatients with MRSA (per various clinical samples)

Total/ Specimen type	Number	Mortality Number (%)
Total (inpatients)	269	28 (10.41%)
Blood	31	12 (38.71%)
Respiratory Specimen	40	15 (37.5%)
Pus	162	1 (0.62%)
Burn Swab	11	0
Eye Swab	9	0
Ear Swab	4	0
Peritoneal Fluid	4	0
Throat	3	0
Synovial	1	0
CSF	1	0
Central Line Cath Tip	1	0
Pleural Fluid	1	0
Urine	1	0

worldwide rate, but indicate a significant increase from the previously reported rate in Bahrain during 2012 of 8.5%[25]. This is ingoing with growing prevalence of MDR problem worldwide[27], Adam et al. also reported an increasing rate of MRSA prevalence in Saudi Arabia to 38% in 2018 from their previous reported rate of 30% in 2012[28].

In the present study, the majority of MRSA isolates was pus (63%) indicating skin & soft tissue infection being the most common clinical presentation of MRSA infection. Among all isolates, there was predilection for Bahraini population and male gender with the maximum number of MRSA isolates was from patients between age group of 25-44 years. Predominance of pus isolates with preponderance of male gender and the age group of 25-44 was in agreement with other previous studies who reported higher incidence of MRSA among young males ranging between 25-44 years old with skin & soft tissue infection being the commonest clinical presentation[29,30.]

Mortality among inpatients with MRSA (all-cause mortality) was 10.4% and in agreement with other previously reported studies[31]. this was more predominant among HO cases with majority of death was encountered among inpatients with bacteremia & pneumonia (blood & respiratory isolates)

In our study, it was noticed that the proportion of CO cases is significantly higher than HO MRSA, which is higher than that been reported by others (10-11), stratifying the data by various clinical samples discloses that preponderance of CO over HO was more predominant among pus, urine, eyes and ears isolates, which might be explained by the fact that skin & soft tissue infection, urinary tract infection, eye and ear infection are commonly managed in outpatient setting.

But we should be very careful in interpreting this high proportion of CO (83%) among all MRSA isolates in our study considering that we included hemodialysis patients (patients attending the two main governmental hemodialysis units in Bahrain) in our study population and they were all encountered as CO as attending outpatient facilities, keeping in mind that patients on hemodialysis are among the high-risk group for MRSA infection.

Hence, such high proportion of CO MRSA should be further analyzed by getting more clinical details of patients with CO-MRSA in future studies to disclose their risk factors and previous exposure to health care system.

LIMITATION OF THE STUDY

The main limitation of the study is the unavailability of important clinical details as being retrospective study and all Information was dependent on the available previous electronic medical records.

Firstly, we limit the definition of health care associated MRSA to Hospital Onset MRSA (HO-MRSA) which is defined in this study as inpatients who develop infection and had positive culture after 48 hours from admission, while for more precise estimation of the burden of health care associated MRSA among Community Onset (CO-MRSA), there would be a need for further sub-classification of community onset cases into its two main distinct categories as Health-care Associated (HA-CO MRSA) and Community Associated (CA-CO MRSA), where HA-CO MRSA is defined as MRSA acquired outside the hospital but among patient with previous exposure to health care system[11,32-33], but such detailed history of previous health care system exposure among our study population was missing which precluded us from having more precise estimation for health care associated MRSA.

The second limitation is the lack of clinical information of the underlying comorbidities & other risk factors among patients infected with MRSA, to identify the important risk factors for MRSA acquisition among our population.

Considering that the majority of MRSA cases in this study was community onset; future focused study on the community onset MRSA in Bahrain should be a priority, with more clinical details about patients to get a precise estimation of its burden with identification of important risk factors for acquisition, as this should play a crucial role in setting an effective prevention and control measures of MRSA at the community level based on our local epidemiological finding.

CONCLUSION

In our study, MRSA prevalence rate in the governmental health care facilities in Bahrain is 22%, with majority of the cases are being community onset and significant proportion is detected among outpatient facilities, such finding necessitate the need for comprehensive preventive and educative strategies to control the increasing MRSA prevalence rate in the community with stress upon public awareness for implementation of community-oriented policies to control the risk of MRSA transmission in the community in addition to reemphasis upon the importance of antibiotics stewardship at the community level .

Also, its crucial to alert practitioners in the primary health centers and outpatient clinic about the importance of MRSA risk factors assessment among their patients and to consider MRSA as potential pathogen among high-risk population in outpatient setting.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflict of Interest: None.

Competing Interest: None.

Sponsorship: RCSI medical students participated in data collection and analysis and writing of the manuscript.

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Ethical Approval: The study was approved by the Secondary Care Research Committee of Salmaniya Medical Complex, Ministry of Health, the Kingdom of Bahrain. The study had no ethical consideration with no need of informed consent as it is a retrospective non-interventional study with no exposure to any patient data.

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