Profile, risk factors, genotype and outcome of *Staphylococcus aureus* catheter related blood stream infection in a Malaysian tertiary hospital

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ABSTRACT

Introduction: *Staphylococcus aureus* is a commonly known causative agent of catheter related bloodstream infections (CRBSI) and complicated CRBSI. This study aimed to detect prevalence of *S. aureus* and complicated *S. aureus* CRBSI, their virulence genes and evaluate their association with development of complicated CRBSI, patient risk factors and outcomes.

Materials and Methods: A cross-sectional study involving retrospective record review of CRBSI cases was conducted from January 2019 to December 2021. A total of 139 CRBSI cases were identified. Patients' clinical data, risk factors and outcomes of *S. aureus* CRBSI were analyzed. Nineteen isolates from patients with complicated *S. aureus* CRBSI were selected for detection of *Cna, Chp* and *Cap8* gene using PCR. The association between the development of complicated *S. aureus* CRBSI and the presence of virulence genes was analyzed.

Results: Forty-three (31%, n=43) of CRBSI cases were caused by *S aureus*. Among these, nineteen cases (44.2%) were complicated. Patients with chronic kidney disease (CKD) or end-stage renal failure (ESRF) (adjusted OR 11.11, 95% CI: 2.86–33.33, p<0.001) were at significant risk of S.aureus CRBSI. Virulence genes detected were *Cap8* (89.5 %, n=17), *Cna* (47.4%, n=9) and *Chp* (26.3%, n=5). The presence of these genes was not significantly associated with the development of complicated *S.aureus* CRBSI. *S. aureus* CRBSI were associated with higher mortality (p=0.035).

Conclusion: *S. aureus* was the predominant agent for CRBSI and 44.2% of them were complicated. CKD/ESRF were the comorbidities associated with *S. aureus* CRBSI. Although cap8 was the most frequently detected virulence gene, it was not associated with the development of complicated *S. aureus* CRBSI.

KEYWORDS:
Staphylococcus aureus; catheter related bloodstream infection; risk factor; virulence gene; complicated catheter related bloodstream infections

INTRODUCTION

The use of intravascular central catheters has become an important component of patient care and management. They function by providing secure access to the circulation for procedures like hemodialysis and administration of medication or chemotherapy. The undesired side effect associated with catheter use is the increase in cases of Catheter Related Bloodstream Infections (CRBSI). In the years 2008 to 2013, the incidence was estimated to be around 30,100 in intensive care units and acute care wards.[1] It poses burden to both patients and the healthcare system as it results in significant mortality, longer hospital stays and higher hospital costs.[2] Among the organisms that cause CRBSI, *S. aureus* was the most frequent isolate.[3] *S. aureus* is a Gram-positive aerobic bacterium that has a niche preference for the anterior nares.[4] Community-acquired *S. aureus* was associated with native and prosthetic valve endocarditis, skin, and soft tissue infections, and osteoarticular infection; while healthcare-acquired *S. aureus* infection was associated with devises or procedure in the form of ventilator-associated pneumonia, CRBSI and surgical site infection.[3] The mortality rate associated with invasive *S. aureus* bacteremia has been found to range between 20-37%.[5-6] Apart from high mortality, *S. aureus* that caused CRBSI also causes complicated CRBSI. Complicated CRBSI is defined according to van der Vaart et al[7] as the presence of either one of the following:

a) Development of endocarditis (according to modified Duke criteria)
b) Septic thrombophlebitis (persistent *S. aureus* bacteremia for >72 hours after the initiation of active therapy associated with the documentation of a thrombus at the site of catheter insertion).
c) Septic metastatic infection, including arthritis, spondylodiscitis, infection involving vascular osteoarticular prostheses or end-organ hematogenous seeding to other location.
d) Persistent bacteremia >72 hours or
e) persistent fever for more than four days after extraction of the first blood culture yielding *S. aureus*, provided that alternative cause had been reasonably excluded.[7] The development of complicated *S. aureus* CRBSI in certain patients but sparing others had led to doubts regarding pathogen factor that affect the different outcome. San-

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Juan et al had demonstrated in their multicenter research the pathogen factor for developing complicated *S. aureus* CRBSI was *Cap*8, *Cna* and *Chp* gene.[8]

The *Cna* gene encodes a collagen binding protein, a structure that is part of the microbial surface components recognizing adhesive matrix molecule (MSCRAMMS) They are cell wall adhesins that function by binding to host collagen. The catheter placement into blood vessel is followed by subsequent coating with patient serum that is rich in fibrin. Collagen will enhance collagen-binding protein expression and contribute to the biofilm formation. Meanwhile the *Cap*8 gene encodes capsule polysaccharide 8, which plays a role in evading the human immune response through its antiphagocytic function. The *Chp* gene encodes a chemotaxis inhibitory protein that impairs the neutrophil recruitment. Data pertaining to the above aspects were limited and therefore, this study objectives of this study were to describe the profile of CRBSI in our health center, analyze the risk factors and outcomes of *S. aureus* CRBSI and identify the proportion of complicated *S. aureus* CRBSI and *S. aureus* virulence genes (*Cap*8, *Cna* and *Chp*), as well as the association between the two.

MATERIALS AND METHODS

This study received approval from local research ethics committee (Reference No: USM/JEPeM/21020189) for data collection from patients' medical record. A cross-sectional study involving retrospective record review of CRBSI cases which were carried out from January 2019 till December 2021 at a tertiary teaching hospital which has a capacity of 800 bedded patients. Convenience sampling was used for sample collection. Inclusion criteria include cases that were clinically diagnosed with CRBSI, and the paired culture result that fulfilled the differential time to positivity between central and peripheral of two hours or more. Exclusion criteria were cases with inadequate clinical history. A total of 139 isolates from cases of CRBSI were collected over the study period. All the *S. aureus* isolate were identified based on phenotypic characteristics; round convex colony with or without beta hemolysis on blood agar, Gram-stain showing Gram positive cocci in cluster, biochemical test catalase, and coagulase positive; and positive with latex agglutination test Staphaurex Plus (Thermo Fisher Scientific, Waltham, U.S.A.). Only methicillin sensitive *S.aureus* (MSSA) will be included in the research. The antibiotic sensitivity testing for methicillin was carried out using disc diffusion (Kirby Bauer) method, with interpretive breakpoint provided by Clinical and Laboratory Standards Institute (CLSI M100 31st edition. All 19 samples of complicated *S. aureus* CRBSI were selected and subjected to exploratory subset analysis using molecular PCR to detect the presence of the gene *Cna, Chp* and *Cap*8.

DNA extraction

Nineteen phenotypically confirmed *S. aureus* colonies were subjected to DNA extraction via DNA lysate boiling method. Two loopful of the colonies were taken from blood agar plate of *S. aureus* incubated overnight in CO_2. It was mixed into 100µl of distilled water and stirred adequately until no sediment was observed. The mixture was then boiled at 100ºC for ten minutes, followed by centrifugation at 12,000 rpm for five minutes to remove all the cell debris. The supernatant formed after centrifugation was transferred into a new tube while the cell debris was discarded. The lysate was then stored and kept in 4ºC while waiting for subsequent PCR analysis.

PCR analysis

Each PCR reaction mixture (total volume 25 µl) was prepared by pipetting 3µl of DNA lysate, 7.5µl distilled water, 1µl of 25 µM forward and reverse primer, 12.5µl of MyTaq Red Mix DNA polymerase buffer (Bioline, Cincinnati, U.S.A). The sequence for the primer used in the study are listed in Table I. The temperature and time required for denaturation and elongation are the same for the three target genes and one housekeeping gene, which were initially denatured at 95ºC for five minutes, with subsequent denaturation at 95ºC for 30 second, annealing at 60ºC for 30 second, elongation at 72ºC for 30 second, followed by final elongation at 72ºC C for 5 minutes. This was followed by 35 cycles of denaturation, annealing, and extension. Post amplification analysis was carried out with gel electrophoresis method by detection of present of band.

Data collection and statistical analysis

The medical record of all the patients diagnosed with CRBSI was retrieved and reviewed. Patient data including demographic information, comorbidity and outcome were extracted from medical records for analysis.

All the data were analyzed using IBM SPSS Statistic version 27. The profile of *S. aureus*, the proportion of virulence gene in complicated *S. aureus* CRBSI and proportion of complicated CRBSI were presented as descriptive statistics. The association between risk factor for *S. aureus* CRBSI were analyzed using univariate analysis, the risk factors with p-value of <0.25 were further analysed using multiple logistic regression. While outcome of *S. aureus* CRBSI and association between complicated *S. aureus* CRBSI with virulence gene were analyzed using Pearson Chi Square.

RESULTS

A total of 139 CRBSI cases were included in the study. Forty-three cases (31%, n=43) were caused by *S. aureus* and nineteen of them (44.2 %) developed complicated *S aureus* CRBSI. The demographic data of study participants is summarized in Table II. The mean age for patient with CRBSI was 46-year-old, with male being slightly more common than female More than half of them have comorbidity of diabetes mellitus and CKD or ESRF. The most common reason for intravascular catheterization was for indication of hemodialysis, and the insertion of catheter over the internal jugular or subclavian chemoport was more frequently seen than femoral catheter.

Staphylococcus aureus was the most frequent organism causing CRBSI followed by another Gram-positive organism which was coagulase-negative *Staphylococcus*. Association between *S. aureus* CRBSI with its risk factors are as shown in Table III. Multiple regression analysis showed that the development of S. aureus CRBSI was significantly associated with patient having CKD/ESRF (adjusted OR 11.11, 95% CI:

2.86–33.33, p<0.001), while hematological malignancy and diabetes mellitus were not significantly associated with *S. aureus* CRBSI. The site of catheter did not have a significant association with development of *S. aureus* CRBSI. With regards to outcome, *S. aureus* CRBSI patient was significantly associated with outcome of death (p=0.035) (Table IV). The mortality rate for S.aureus CRBSI is this study was 32.6% (95% CI : 18.6- 46.6%). About 15.9% of the risk of death in CRBSI can be attributed to the *S. aureus* infection, compared to the control group.

All nineteen cases of complicated *S.aureus* CRBSI were selected for molecular detection of virulence gene namely *Chp, Can* and *Cap*8.The results were as shown in Figure 1a and b. *Cap*8 gene was most commonly present (n=17,89%) followed by *Cna* gene (n=9, 47%) and *Chp* gene (n=5,26%).

DISCUSSION

In this retrospective analysis of over a three years duration in patients diagnosed with CRBSI, *S. aureus* was found to be the most common etiological agent. This finding is in accordance with other studies that describe the common pathogen causing CRBSI.[9] However, some studies showed a decreasing trend in cases of *S. aureus* causing CRBSI.[10]

There are limited Southeast Asian studies specifically focusing on complicated S.aureus CRBSI and bacteremia. A Singapore tertiary-hospital study of 100 patients with community-onset MSSA bacteremia found that 46% developed complicated bacteremia and 18% developed infective endocarditis. The attributable mortality was 11%.[11]

Intravascular access over internal jugular vein was usually preferred over femoral vein due to its direct path into superior vena cava and hence is less technically challenging. It is also more convenient for the patient to ambulate and move around. Thus, it was not surprising that it was being used more commonly in this study compared to femoral catheter. A published randomized controlled trial that compared the site of intravascular catheterization between jugular vein and femoral vein found that the rates of CRBSI (2.3 vs. 1.5 per 1000 catheter days, respectively; p=0.42) and catheter colonization (35.7 vs. 40.8 per 1000 catheter days, respectively; p=0.031) were similar in both groups.[12] This explains the finding where the site of vascular access was not found to be significantly associated with *S. aureus* CRBSI.

Renal replacement therapy has become a life-sustaining option for patients with renal failure. The 26th Report of the Malaysian Dialysis and Transplant Registry 2018 revealed that haemodialysis was a more common choice compared to peritoneal dialysis, where among 8431 newly dialyzed patient, 7200 used hemodialysis while 1231 patients used peritoneal dialysis.[13] Among the three types of vascular access for haemodialysis, namely arteriovenous fistula, arteriovenous graft and central venous catheter, the latter was less desired due to complications including catheter-related infection. In the HEMO study, a multicenter randomized clinical trial designed to evaluate the effect of haemodialysis dose and flux on morbidity and mortality, access-related infection was present in 32% of study patients despite central venous catheter being used for 7.2% of vascular access.[14] The increase in negative outcomes associated with central venous catheters was also shown in a systematic review of 62 cohort studies, where individuals using catheters had higher risks for fatal infections when compared to those with fistula (2.12, CI 1.79–2.52) and to those with graft (1.49, CI 1.15–1.93).[15] The microorganism that was responsible for CRBSI among renal failure patients was commonly found to be *S. aureus*, as shown from a literature published by one of the local university hospitals as well as a 12-year review from a tertiary referral hospital.[16-17] This finding was in concordance with the result from this study that showed statistical association between *S. aureus* and patients with CKD or ESRF. Apart from catheter-related bacteraemia, the nasal carriage rate of *S. aureus* was also high among dialysis patients and can be found in up to 41% of the cases.[18] This colonization eventually became the route of acquiring *S. aureus* CRBSI where the infection was endogenously acquired.[19] A genotypic study was able to demonstrate the correlation where in more than 80% of the cases of bacteremia strain was genotypically similar to the strain carried in the patient's nasal cavity.[20] This correlation had led to the use of antimicrobials for nasal eradication of the *S. aureus* reservoir, and a meta-analysis showed that the use of mupirocin for eradication was associated with a 59% (cpRR, 0.41; 95% confidence interval [CI], 0.36–0.48) reduction in *S. aureus* infection among dialysis patients.[21]

Diabetes mellitus is a metabolic disease with potential systemic complication. It affects the innate and acquired immunity and causes patients to become susceptible to infection.[22] However, the association between diabetes and developing *S. aureus* bacteraemia due to CRBSI was less straightforward. The association between the two was found in a retrospective study carried out in a university-affiliated hospital.[23] However, the diabetic patients included in the study were also dialysis-dependent (as discussed earlier, ESRF was associated with *S. aureus* CRBSI), and only univariate analysis was done causing it to be affected by other confounding variables. This was seen in our study where the association between the two was statistically significant with Pearson Chi Square test but found to be insignificant when using multiple logistic regression.

A recent retrospective study that compared two groups of cancer patients from 1999 to 2000 and 2013 to 2014 that was published by Chaftari et al showed that Gram-negative organism made up 41% of the CRBSI cases.[24] Furthermore, another study demonstrated the change in epidemiology of causative organisms from predominantly Gram-positive to Gram-negative.[25] This was in concordance with our study that found *S. aureus* to be not significantly associated with CRBSI in patients with hematological malignancy.

S. aureus bacteraemia is known to be associated with substantial mortality. In a study where nosocomial *S. aureus* bacteraemia was predominantly catheter-related (61%), the mortality rate was found to be 20%.[26] Another ten-year prospective cohort study showed that CRBSI cases with *S. aureus* as the etiological organism were associated with significant mortality. This was in accordance with the findings from this study.[27]

Table I: List of Primers used for the optimization of PCR Assay

Target gene	Sequence	Primer size	Reference
Chp- F	5′- ACG GCA GGA ATC AGT ACA CA- 3′	291	de Haas CJ et al 2004
Chp- R	5′- TCT ATC TTC AGC AAG TGG TGT- 3′	291	
Cap 8- F	5′- TGG CGC AAG AGG TTC AAA GT-3′	307	Sau, S et al year 1996
Cap 8- R	5′- ACT GCT GTA CCG TCT GCT TT- 3′	307	
Cna- F	5′-CCA AGG CTC CTA TAG CTA ATG T -3′	310	Yamamoto et al., 2006
Cna- R	5′-TGA GTG CCT TCC CAA ACC TT -3′	310	
Arc- F	5′-TTG ATT CAC CAG CGC GTA TTG TC -3′	456	Buttimer et al 1995
Arc- R	5′-AGG TAT CTG CTT CAA TCA GCG -3′	456	

Table II: Demographic data of CRBSI cases during the study period.(n=139)

Variable	Frequency (n,%)
Age (Mean)	46
Gender	
Male	78
Female	61
Comorbidities	
Diabetes mellitus	77, 55%
Chronic kidney disease/End stage renal failure	77, 55%
Solid tumour	14, 10%
Haematological malignancy	25, 18%
Catheter Site	
IJC catheter	84, 60%
Femoral catheter	55, 40%
Indication for catheterization	
Antibiotic	23, 17%
Chemotherapy	32, 22%
Haemodialysis	76, 55%
Total Parental Nutrition	8, 6%
Microorganisms	
Staphylococcus aureus	43, 31%
Coagulase negative Staphylococci	21, 15%
Other Gram positive organisms	17, 12%
Enterobacterales	24, 17%
Non Enterobacterales	23, 17%
Yeast	11, 8%
ICU admission	
Yes	33, 24%
Nil	106, 76%
Outcome	
Death	109, 22%
Survive	30, 78%

Table III: S. aureus CRBSI with its associated risk factors

	Crude ORa (95% CI)	p-value	Adjusted ORb (95% CI)	p-value	Wald statistics (df)	p-value
Chronic kidney disease/ End stage renal failure	11.1 (4.0, 30.7)	<0.001	11.11 (2.86–33.33)	<0.001	12.19	<0.001
Non chronic kidney disease/End stage renal failure	1.0		1.0			
Diabetes mellitus	3.4 (1.6, 7.6)	0.02	0.9 (0.3,2.6)	0.889	0.02	0.889
Non diabetes mellitus	1.0		1.0			
Haematological malignancy	0.16 (0.04, 0.69)	0.06	1.0 (0.15,6.84)	0.989	<0.01	0.989
Non haematological malignancy	1.0		1.0			
Femoral catheter	0.137 (0.19,0.139)	0.137	-	-	-	-
Non femoral catheter	-	-	-	-	-	-

*Simple logistic regression and multiple logistic regressionb was applied. All the assumption met (Classification table=69.1; Hosmer Lemeshow value=0.74; Area under the curve ROC=0.74(0.83,0.66)
Adjusted OR 11.11 (95% CI: 2.86–33.33).

Table IV: S. aureus CRBSI with its associated outcome

	Staphylococcus aureus	Non-Staphylococcus aureus	X^2(df)	p-value
Death	14	16	1	0.035
Survive	29	80		

Attributable Risk = 0.326–0.167=0.159 (15.9%)
Mortality rate = 32.6% (95% CI = 18.6% - 46.6%)

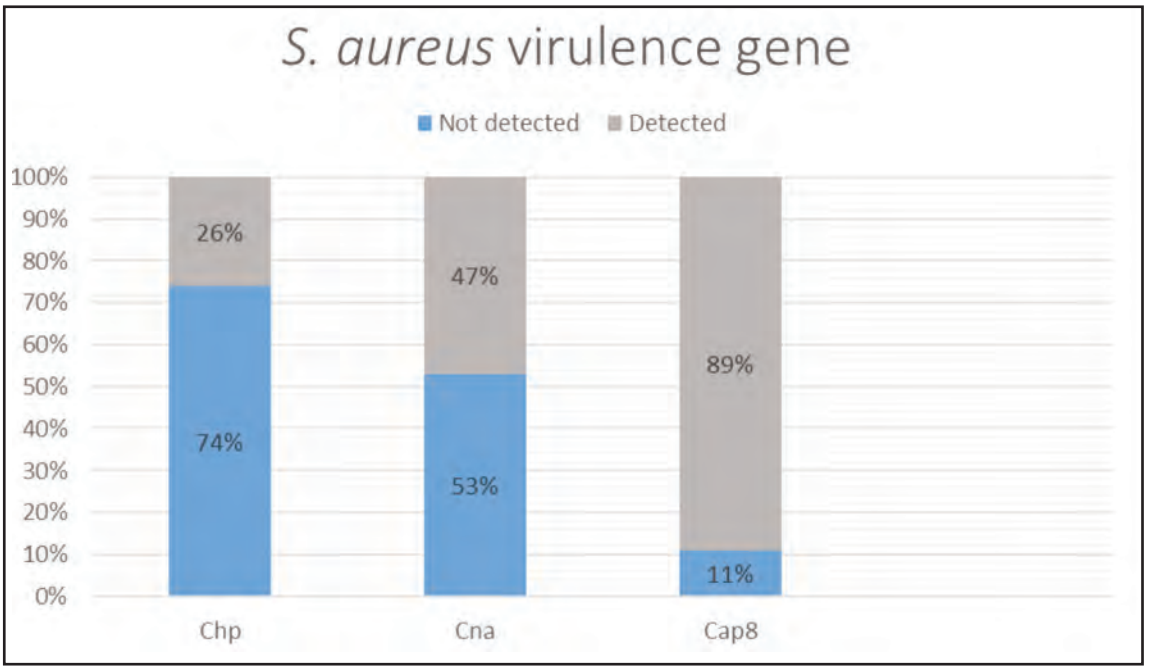

Fig. 1a: Virulence gene detected among selected *S. aureus* CRBSI (n=19)

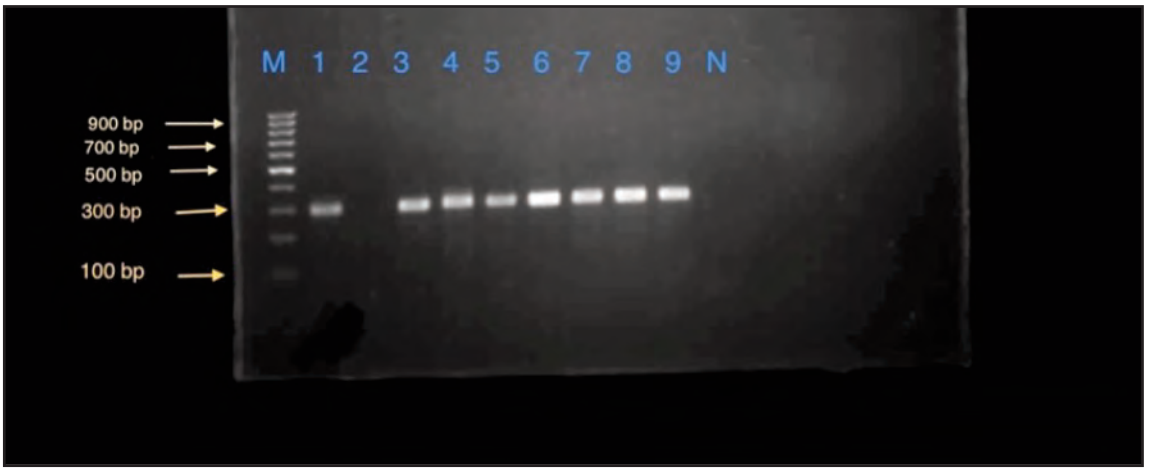

Fig. 1b: Representative image of agarose gel electrophoresis of monoplex PCR assay targeting *S.aureus* DNA amplicon using virulence gene Cap8 primer
Lane M: 100bp DNA ladder, Lane 1: STAU 001, Lane 2:STAU 002, Lane 3:STAU 003, Lane 4:STAU 004, Lane 5:STAU005, Lane 6:STAU 006, Lane 7:STAU 007, Lane 8:STAU 008, Lane 9: STAU 009, Lane N: Negative control

Patients without complicated CRBSI were more frequent than patients with complicated CRBSI, with this study recording 44.2% among *S. aureus* CRBSI patients, a percentage higher than that recorded by San-Juan et al[8] of 31.3%. However other findings like the most common virulence gene (*Chp* gene in San-Juan et al[8], *Cap*8 in this study) and the association between the three virulence genes and the development of complicated CRBSI (*Chp, Cna, Cap*8 respectively was not found to be statistically significant in this study) could be due to the molecular detection being only an exploratory subset analysis in a single center study with smaller sample size.

S.aureus colonization has several important implications in healthcare. This study showed that patients with renal failure have a significant risk of developing *S. aureus* CRBSI. This group of patients with ESRF may benefit from nasal swab screening for *S. aureus* colonisation. The same applies to other immunocompromised patients such as patients with malignancy. This is supported by published systematic reviews and meta-analyses indicating that nasal screening for *S. aureus* in haemodialysis patients could help to identify carriers, and when combined with decolonization therapy, could significantly reduce catheter infections and bloodstream infections.[28-29]

CONCLUSION

This study shows that CKD or ESRF was the comorbidity associated with the development of *S. aureus* CRBSI. Complicated *S. aureus* CRBSI contributed about 44.2% of total *S. aureus* CRBSI. The most common virulence gene was *Cap*8. The retrospective design, single-center setting and small genotypic sample size could be the limiting factors for finding significant association between the virulence gene and complicated CRBSI.

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