Group B Streptococcal bacteraemia - Changing trends in a tropical region of Australia

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Abstract

Background

Group B streptococcus (GBS) is a recognised perinatal and neonatal pathogen**.** There are reports of increasing GBS sepsis globally outside this demographic. North Queensland is part of tropical Australia, with a relatively high proportion of Indigenous Australians. Group A streptococcal (GAS) sepsis is well recognised and overrepresented in this population.

Aims

This study aims to analyse the epidemiology of GBS bacteraemia and explore the changing trends relative to GAS .

Methods

This was a 10-year retrospective review of GBS bacteraemia in a tertiary facility in North Queensland, between 2010 and February 2020. Data variables collected included; demographics, risk factors, clinical source and outcomes. Statistical analysis included Kaplan-Meier curves to characterise all time-to-event variables and Cox proportional hazard models. Inference was based on a 5% level of significance.

Results

Of the 164 total cases, 123 were not pregnancy related. The rate of GBS bacteraemia for the Indigenous population was 124.77 per 100, 000 and 48.36 per 100, 000 for the non-Indigenous population. Obesity and diabetes were overrepresented co-morbidities. Malignancy was associated with an increased mortality. Similar to invasive GAS disease, soft tissue infections was the commonest source of GBS bacteraemia accounting for 43.1% of cases.

Conclusion

GBS bacteraemia is deviating from being primarily a neonatal disease. While the Indigenous population of North Queensland have a disproportionate burden of both GAS and GBS disease, the populations affected differ. GBS appears to target the older non-Indigenous patient with greater comorbidities. In the non-Indigenous population, GAS is uncommon but invasive GBS disease is an emerging issue.

Introduction

Streptococcus agalactiae, group B streptococcus (GBS), is a Gram-positive encapsulated beta haemolytic streptococcus, that belongs to the group of pyogenic streptococci.[1] It is a common coloniser of people of all ages and is generally found in the gastrointestinal tract, vagina and urethra.[2] GBS is becoming an increasingly important cause of invasive bacterial disease globally. Traditionally it is considered to be a neonatal pathogen[3]; however studies have shown an increasing burden of invasive GBS infections amongst non-pregnant adults, particularly in multi-comorbid older adults.[4, 5, 6] In the era of intrapartum antibiotic prophylaxis and enhanced screening techniques, the incidence of neonatal GBS disease has dramatically declined.[7]The most common underlying conditions noted for invasive GBS infection include both diabetes mellitus, particularly with poor glycaemic control, and obesity.[4, 8] Other known risk factors include; neurologic disease, renal failure, malignancies, liver cirrhosis, HIV infection and intravenous cannulation.[9] GBS can cause a wide array of clinical disease including bacteraemia without focus, skin/soft-tissue and osteo-articular infections, pneumonia, urosepsis, endocarditis, peritonitis, meningitis, and streptococcal toxic shock syndrome.[5]

Amongst the non-pregnant adults in the United States of America, the annual incidence of invasive GBS infections has increased from 8 per 100, 000 people in 2008 to 11 per 100, 000 people in 2016. [4, 10] This increase in incidence has been reported to be more pronounced in those aged 65 years or older.[6, 10, 11]Despite this, little is known about the changing trends of invasive GBS disease in Australia. This is especially so in the non-pregnant and non-neonatal population. Townsville Hospital and Health Service caters for a population of approximately 229, 000 and is the major tertiary referral centre for North Queensland. [12] The health service

is one of the most geographically dispersed catchments, extending west to Richmond and Hughenden, north to Cardwell, south to Home Hill and east to Magnetic and Palm Islands. The region has a population with approximately 6.1% - 7% being of Aboriginal and/or Torres Strait Islander descent. [13] In 2010, a study by *Harris et al* evaluated the epidemiology of β-haemolytic streptococcal bacteraemia over a 14-year period (1996-2010) within the Townsville Hospital and Health Service. This study revealed that there was a significant increase in the incidence of non-neonatal bacteraemia caused by GBS, largely driven by infection in older, non-indigenous women. This study also noted the relatively low incidence of invasive GBS in Indigenous Australians, despite the burden of well-recognized risk factors for GBS disease within this population.[14]

The purpose of this study was to examine the changing epidemiological trends of GBS bacteraemia in North Queensland. It aims to provide an overall contemporary epidemiological perspective of GBS bacteraemia within the region. It specifically explores non-pregnant and non-neonatal groups (Indigenous and non-Indigenous); highlights predictors of mortality and will provide some insight into relevant risk factors associated with GBS disease.

Materials and Methods

Study population and study site

This retrospective study evaluated all patients admitted to the Townsville University Hospital and Health service (TUHHS) with a positive blood culture for Group B Streptococcus between 1 January 2010 and 29 February 2020. Patients managed outside TUHHS, in private hospitals, and patients deceased prior to the identification of a positive blood

culture were excluded. The Townsville University Human Research Ethics Committee provided ethics approval for this study (HREC/QTHS/62148).

Data Collection

We identified and extracted data from hospital records and electronic charts as well as from the AUSLAB Pathology Queensland laboratory database for the period under study. Two investigators independently reviewed the identified cases for inclusion in the study. The following variables were collected; patient demographics (ethnicity - dichotomised as Indigenous and non-Indigenous, age, gender, smoking status, and alcohol consumption), pre-existing co-morbidities, season of diagnosis, source of acquisition, presence of prosthetic devices prior to bacteraemia, and one and three-month mortality from the date of diagnosis (positive blood culture). Mortality was determined, on whether the patient was deceased or alive upon a specific time period post admission or bacteraemia. This was determined from a health provider portal, called The Viewer. Census data was obtained from the Australian Bureau of Statistics (ABS).[12]

Statistical analysis

Data analysis was performed in STATA (StataCorp LLC. 2017. Stata Statistical Software: Release 16.1 College Station, TX, USA). Descriptive summaries for continuous variables were computed as means and standard deviation (SD) and counts and percentages for categorical variables.

Chi-square and/or Fisher's exact test were used to compare participant's baseline demographic and clinical characteristics. The association between the exposure variables

including ethnicity, gender, age, excess alcohol consumption, smoking status, and clinical presentations with the mortality at three months (90 days) were assessed. The model was adjusted for explanatory variables with p-value ≤ 0.2 in preliminary univariate analysis. Multivariable Logistic regression with robust standard error was used to investigate the magnitude of associations between mortality at three months and covariates including Indigenous status, gender, and age. Adjusted odds ratio (AOR) estimates and 95% confidence interval are presented. Overall, inference was based on a 5% level of significance.

Results

Demographic Characteristics

Over the 10-year study period, there were a total of 164 cases, of which 27 were neonates (16.5%), 6 were pregnant (3.7%) and 8 were excluded (4.9%). Hence, a total of 123 non-pregnant/non-neonate cases (74.6%) were included in this study. Indigenous [Aboriginal or Torres Strait Islanders or both] patients comprised 17.2% (21) of the total whereas Non-Indigenous patients made up the rest [82.9%, 102]. Of the excluded cases, 7 were due to inability to access medical records, and 1 excluded due to it being a post-mortem sample. Table 1 presents baseline demographics. Gender distribution was similar, total proportion of males (50.4%) and approximately one fifth (17.2%) were Indigenous. Roughly half (50.4%) of the patients were aged between 69-94 years old. In this study, Indigenous patients (mean age in years 51.1, SD 13.3) were significantly younger than their non-Indigenous counterparts (mean age in years 69.4, SD 15.8), t (121) = -4.981, $P < 0.001$. On average Indigenous patients were 18.4 years younger than non-Indigenous patients, 95% CI (11.1-25.7). As shown in Table 1, we also noticed that Indigenous patients had significantly higher

rates of smoking (66.7% vs 41.2%) $\chi_1^2 = 4.402, P = 0.036$. However, the proportion of obesity and excess alcohol consumption were similar between the two groups.

The age, gender, and indigeneity distribution of GBS bacteraemia is shown in Figure 1. The annual rate for GBS bacteraemia for the local North Queensland Indigenous population compared to the non-Indigenous population was 12.48 per 100 000 and 4.84 per 100 000 respectively.

The incidence of GBS bacteraemia over the years amongst neonate, pregnant and non-neonate/non-pregnant cases in Indigenous and non-Indigenous populations is represented in Figure 2. The incidence of GBS bacteraemia in non-neonate/non-pregnant cases is increasing, whilst in the neonate and pregnant population there has been a steady trend.

Clinical characteristics

Table 2 presents the clinical characteristics of the included patients. Indigenous patients were more likely to be diabetic $(85.7\% \text{ vs } 41.2\%)$, $\chi_1^2 = 13.826, P < 0.001$ and have chronic kidney disease (CKD) $(42.9\% \text{ vs } 16.7\%)$, $\chi_1^2 = 7.166, P = 0.007$ compared to non-Indigenous patients. There were no statistically significant associations with the rates of chronic liver disease, malignancy, neuronal disease, and lung disease compared between the two groups on univariate analysis. The most common source for GBS bacteraemia found was cellulitis (55.2%) followed by urine (16.7%), and this was consistent in both groups. There were 8 deaths within 30 days (6.5%), and 16 deaths within 3 months (13.0%) that were associated with GBS bacteraemia. Of the 8 deaths that occurred within 30 days, 4.8% were Indigenous and 6.9% were non-Indigenous. On univariate analysis, we did not find a

statistically significant difference in the rates of mortality due to GBS bacteraemia at three months between Indigenous and non-Indigenous patients (p-value 1.000).

Our study had 8 recurrent cases of GBS bacteraemia. A mean age of 69 years was noted amongst this group compared to 66 years in the non-recurrent cases. All 8 cases were non-Indigenous and 6 of these cases (75%) were females. Half of these cases had a malignancy and 2 were deceased within 30 days. 5 cases (62.5%) had their source of infection for at least one of their episodes as cellulitis. All had multiple co-morbidities and recurrences occurred between 33 days and 4 years from the initial disease.

Multivariable Analysis

Multivariable logistic regression was performed to examine the risk factors of mortality at three months from GBS bacteraemia. All clinically relevant variables including those with P-value ≤ 0.2 in the univariate analysis were included in the multivariable analysis. At the end, the explanatory variables that were found to be associated with mortality at three months from GBS bacteraemia were retained in the multivariable analysis. Table 3 presents the results from the multivariable analysis. Indigenous patients were less likely to experience mortality at three months from GBS bacteraemia [AOR = 0.82, 95% CI (0.10, 6.58), P=0.855] adjusting for other covariates. The Wald test provided insufficient evidence of this association. Compared to females, males were more likely to experience mortality at three months from GBS bacteraemia [AOR = 4.34, 95% CI (1.14, 16.56), P=0.031]. Compared to non-immunosuppressed patients, immunosuppressed patients were more likely to experience mortality at three months from GBS bacteraemia [AOR = 11.49, 95% CI (2.73, 48.42), P<0.001. For each unit increase in age, there was a 2% increase in odds of death

from GBS at three months, [AOR = 1.02, 95% CI (0.96, 1.09), P=0.450], but there is insufficient evidence of this association. In our analysis CKD, diabetes and lung disease did not have a statistically significant impact on mortality at three months from GBS bacteraemia.

Discussion

This study is a retrospective review of Group B streptococcal (GBS) bloodstream infection (BSI) over a 10-year period between January 2010 and February 2020 in tropical North Queensland. As previously mentioned, a total sample size of 123 non-pregnant/non-paediatric patients with GBS bacteraemia were identified in the study period. This specific group was analysed.

A previous study with prospectively entered data in North Queensland between 1996-2010 analysing rates of streptococcal bacteraemia in this region showed the rates for GAS bacteraemia in the Indigenous population was 655.33 per 100,000 compared to 44.45 per 100,000 for the non-Indigenous for the 14-year period. When looking at GBS bacteraemia rates, this same prospective study showed 90.84 and 47.41 per 100,000 for Indigenous and non-Indigenous groups, respectively, over the same time period[14,15] In this study, the rate of GBS BSI for the local North Queensland Indigenous population for the 10-year period was found to be 124.77 per 100,000 people. The rate over the same period for the non-Indigenous population was 48.36 per 100,000 people. There was no gender difference identified. This data indicates that GBS bacteraemia incidence is increasing in the region. This phenomenon has also been reported in studies in multiple European countries, the United States, Canada and the United Kingdom which have shown higher incidence rates of invasive GBS disease among persons aged 65 or older compared to the general, non-pregnant adult population.[17-20] An ageing population confounded with a greater presence of comorbidities would explain this rising incidence of invasive GBS globally.

GBS appears to be occurring at higher rates in the Indigenous population in this region in comparison to the non-Indigenous population. Reasons for this may include the Indigenous community having an increased risk of developing chronic illnesses including diabetes[21],

which may be an associated risk factor for streptococcal disease, as well as issues relating to the cultural and social determinants of health.[22, 23] Moreover, increased work in recent decades to facilitate engagement through strong relationships between Indigenous people and healthcare providers may also be a contributing factor to the rising incidence due to increased detection rates.[24, 25]Despite this study demonstrating higher rates of GBS bacteraemia in the Indigenous North Queensland population in comparison to non-Indigenous, this finding appears to dissipate with increased age (as shown in Figure 1). The mean age for GBS BSI in this study was 66.1 years. This compares with a mean age of 45 for GAS BSI in a previously reported study.[14] This increased average age for GBS BSI in this population may be related to the presence of comorbidities such as CKD, obesity and diabetes, as well as increased life expectancy and an ageing population - all of which are known risk factors for GBS infection.[15] As previously mentioned, as age increased there appeared to be a predilection towards non-Indigenous cases rather than Indigenous. This may be due to the fact that Indigenous Australians have a life expectancy 17 years less than non-Indigenous Australians and a burden of disease 2.5 times greater.[23, 26] Moreover, rates of diabetes in the Indigenous population have been well-established to be increased when compared to the non-Indigenous population.s[21] The Australian Institute of Health and Welfare reports that Indigenous Australians are four times as likely to have type 2 diabetes prevalence, hospitalisation and death rates as their non-Indigenous counterparts.[27] Although serious invasive GBS disease can occur in adults who are otherwise in good health, the majority of disease occurs in those with significant underlying conditions.[15, 28] Over 50% of subjects in this population had a body mass index (BMI) of >30 and a similar proportion had diabetes. It is known that diabetes and obesity both individually predispose to infections, especially skin and soft tissue infections, which this study showed to be the most

frequent source.[29, 30] These conditions have been described as risk factors in GBS disease in various previous studies. Furthermore, the proportions of affected individuals who have these risk factors is comparable to that seen in other studies.[3-4, 15, 31-32] The prevalence of diabetes and obesity is also increasing in Australia and together with an ageing population, could explain the increased rate of GBS disease in these populations.[32, 33]

It was noted that smoking was significantly higher in the Indigenous group compared to the non-Indigenous group. With respect to smoking being a risk factor for GBS disease, a number of hypotheses for this exist. Firstly, smoking increases the risk of peripheral vascular disease, which subsequently increases the risk of skin and soft tissue infections (SSTIs) in patients[34, 35], which this study showed was the commonest source of infection. Secondly, smoking also affects neutrophil function and is widely known to alter immune functions and compromise host defence against microbial infection.[36]

When comparing risk factors between Indigenous and non-Indigenous populations almost all risk factors assessed were comparable except that of diabetes and CKD. The proportion of the Indigenous population that were diabetic was more than double compared to the non-indigenous population in this study. This is reflected in the prevalence rates here in Australia of diabetes in the Indigenous population in that they are three times more likely to be affected compared to the non-Indigenous population. CKD was defined as a glomerular filtration rate of less than 60 in this study (i.e. stage 3 and higher). The proportion of the Indigenous population with CKD in this study was also more than double their non-Indigenous counterparts. Again, when comparing with prevalence rates in Australia, Indigenous Australians were twice as likely to have biomedical signs of CKD as the non-Indigenous population.[37] As previously mentioned, this may explain the increased rates of streptococcal disease in the Indigenous population.[38]

In common with invasive GAS disease, skin and soft tissue infection was the commonest source accounting for 43.1% of cases overall. This predominance of skin and soft tissue as the primary source of infection for GBS BSI is well-described in both local and worldwide literature.[14, 28] When comparing sources of infection between Indigenous and non-Indigenous populations there were few differences, and analysis showed that skin and soft tissue infection remained the most common source between the two populations.

As outlined in the results, a total of 8 cases were noted to be recurrent disease states. Recurrent GBS BSI was defined as the re-isolation of GBS from blood after 30 days of targeted and appropriate antibiotic therapy and source control, where applicable. All were non-Indigenous, had co-morbidities and had a mean age of 69 years compared to 66 years in the non-recurrent population. This phenomenon is not seen commonly with GAS BSI and appears to be a feature of the older non-Indigenous patient. Recurrent GBS disease has been described in previous studies and accounts for as many as 4.3% of cases which was comparable to the population in this study.[28]

When observing the results on mortality in our population, there were 8 deaths within 1 month and 14 within 3 months from time of positive blood culture, with the majority of these cases occurring in the non-Indigenous population. Immunosuppression was determined to be an increased risk factor for 3-month mortality when compared to non-immunosuppressed patients. This is expected given that those that are immunosuppressed are more at risk of complications and adverse outcomes from infections. Patients were

considered to be immunosuppressed if they were on high dose steroids (>20mg/d), had active cancer, were HIV positive, or on chemo/radiotherapy.

Males were more likely to experience mortality at 3 months compared to their female counterparts, when adjusting for other risk factors. The reason for this remains uncertain, however it is well-recognised that males typically engage in risky health behaviours more often than females and are more likely to die prematurely due to experiencing different health outcomes to Australian females[39].

There are some limitations to this study. This is a retrospective review of GBS bacteraemia and as with all retrospective studies, the assessment of the potential source of the infection is dependent upon a variety of clinicians. Furthermore, there are limitations regarding administrative data that are important to recognise, and subsequent data collection is limited by the completeness of medical records. Identification of cases was limited to those that had presented to the district's major public hospital and did not take into account presentations to peripheral rural hospitals, private practice or private hospitals unless stated in medical records. This allows for some selection bias, as certain populations or demographic groups may present to rural hospitals or private hospitals which might have affected the incidence of GBS BSI in different group subsets. The population in surrounding towns that would have been missed would be small and any cases that were missed would not have influenced the conclusions. In particular, acute admissions for sepsis to the single private hospital in the region, is uncommon.

Determination of mortality, and the cause of mortality were similarly limited due to poor documentation and the mortality of patients outside of hospital. This would make the cause of death difficult to attain. Isolates were also not available for molecular typing. Relatedness therefore cannot be determined, and this is particularly true of recurrences.

Conclusion

This study has shown that while the Indigenous population of North Queensland have a disproportionate burden of GBS, the demographics affected differ. Despite GBS affecting the Indigenous population to a greater extent than their non-Indigenous counterpart, GBS appears to target the older non-Indigenous patient with greater comorbidities. In the non-Indigenous population, invasive GBS disease is an emerging issue. It also revealed that Indigenous patients were more likely to be diabetic and have CKD compared to the non-Indigenous patients. Finally the study has demonstrated a greater 3-month mortality in males compared to females, as well as highlight the increased mortality risk associated with immunosuppressed patients.

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Figure 1: GBS bacteraemia episodes in NQ from 2010-2020 by age group, sex and indigenous status:

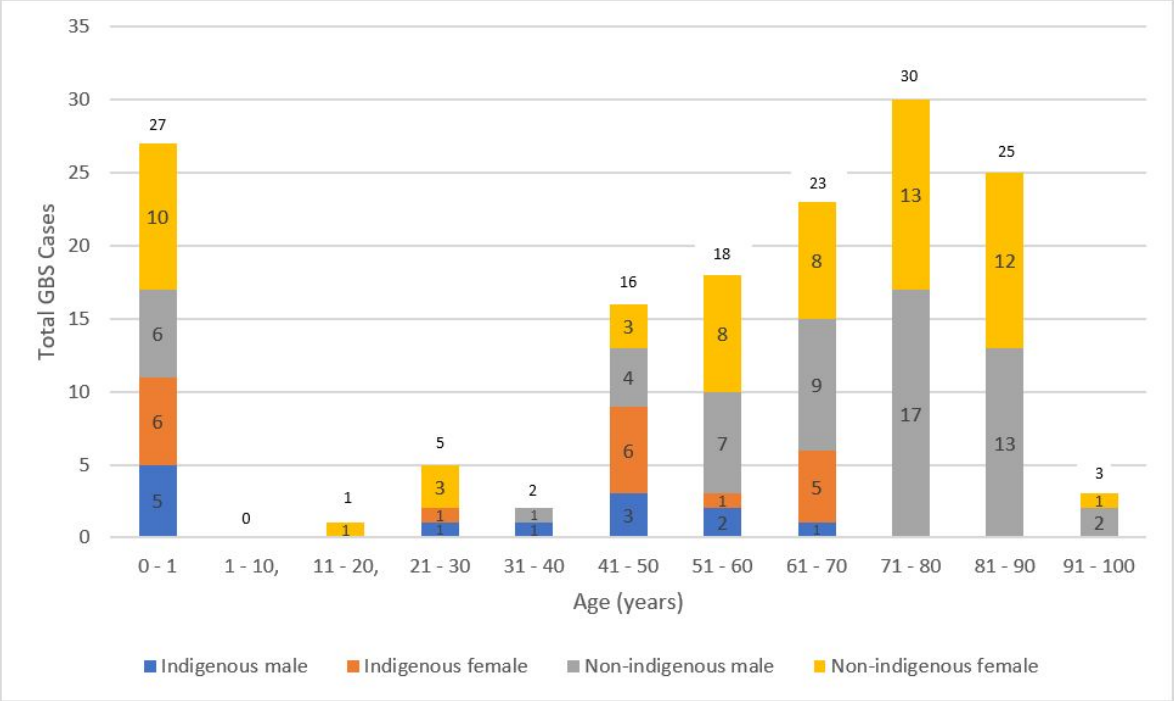

Figure 2: Incidence of GBS bacteraemia episodes in NQ in neonates, pregnant and non-neonate/non-pregnant (indigenous and non-indigenous) cases during 2010-2019

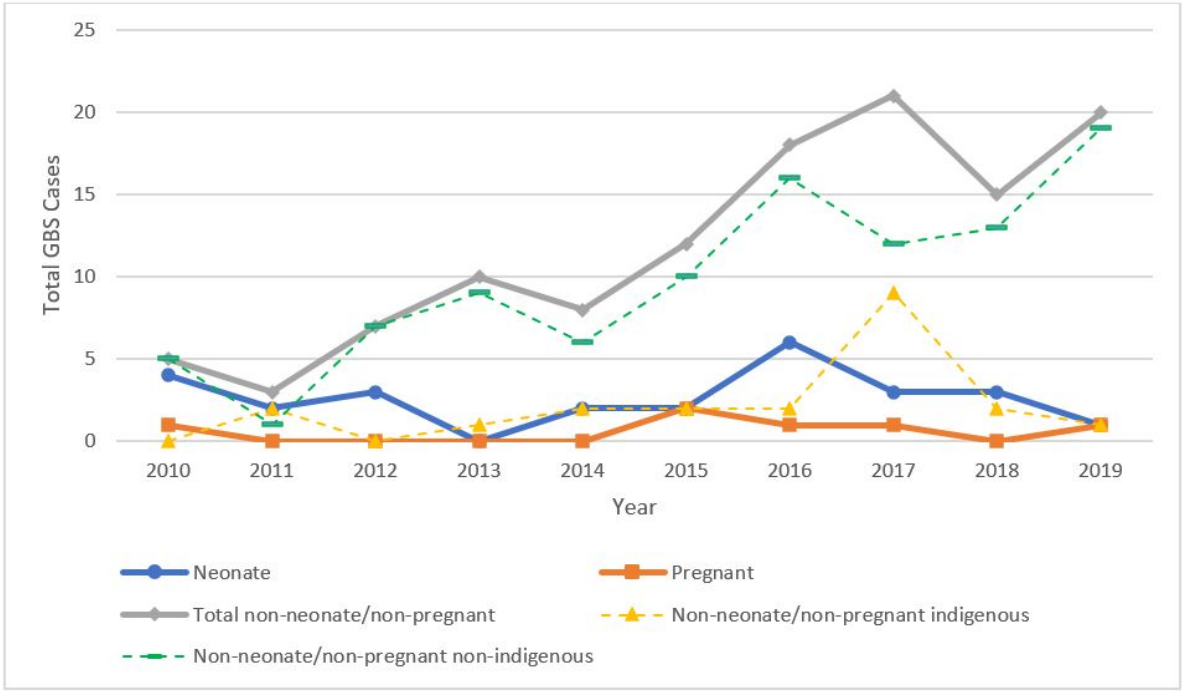

Table 1: Population characteristics.

	INDIGENOUS (%) OR MEAN (SD) (N = 21)	NON-INDIGENOUS (%) OR MEAN (SD) (N = 102)	TOTAL (%) OR MEAN (SD) (N = 123)	P-VALUE
AGE	51.1 (13.3)	69.4 (15.8)	66.3 (16.9)	**<0.001**†
OBESITY	10 (47.6)	54 (59.3)	64 (57.1)	0.328
MALE	9 (42.9)	53 (52.0)	62 (50.4)	0..447
EVER SMOKED	14 (66.7)	35 (41.2)	49 (46.2)	**0.036**
PROSTHETIC DEVICE	1 (4.8)	21 (20.8)	22 (18.0)	0.118‡
EXCESS ALCOHOL CONSUMPTION	5 (26.3)	14 (16.7)	19 (18.5)	0.327

All Chi Squared test, Column percentages presented

†**= Student T-test**

‡**=Fisher's exact test**

Table 2: Descriptive summaries of clinical presentation of patients in this study

	INDIGENOUS (%) OR MEAN (SD) (N = 21)	NON-INDIGENOUS (%) OR MEAN (SD) (N = 102)	TOTAL (%) OR MEAN (SD) (N = 123)	P-VALUE
CHRONIC KIDNEY DISEASE	9 (42.9)	17 (16.7)	26 (21.1)	**0.007**
DIABETES	18 (85.7)	42 (41.2)	60 (48.8)	**<0.001**
CHRONIC LIVER DISEASE	3 (14.3)	9 (8.8)	12 (9.8)	0.429†
IMMUNOSUPPRESSION	4 (19.1)	9 (8.8)	13 (10.6)	0.234†
MALIGNANCY	3 (14.3)	34 (33.3)	37 (30.1)	0.117†
NEURONAL DISEASE	3 (14.3)	24 (23.5)	27 (22.0)	0.563†
LUNG DISEASE	4 (19.1)	16 (15.7)	20 (16.3)	0.747*
SOURCE				
Cellulitis	8 (40.0)	45 (59.2)	53 (55.2)	
Urine	4 (20.0)	12 (15.8)	16 (16.7)	
Respiratory	1 (5.0)	7 (9.2)	8 (8.3)	
Gastrointestinal	1 (5.0)	6 (7.9)	7 (7.3)	
Arthritis	1 (5.0)	3 (4.0)	4 (4.2)	0.106
Line infection	2 (10.0)	1 (1.3)	3 (3.1)	
Sub-acute bacterial endocarditis	1 (5.0)	1 (1.3)	2 (2.1)	
Endometrial (non- pregnant)	0 (0)	1 (1.3)	1 (1.0)	
Genitourinary	1 (5.0)	0 (0)	1 (1.0)	
Diabetic foot infection	1 (5.0)	0 (0)	1 (1.0)	
30 DAY MORTALITY	1 (4.8)	7 (6.9)	8 (6.5)	1.000†
90 DAY MORTALITY	2 (9.5)	14 (13.7)	16 (13.0)	1.000†

All Chi Squared test, Column percentages presented

†**=Fisher's exact test**

Table 3: Multivariable analysis of determinant factors for GBS associated mortality within 90 days

RISK FACTOR	ADJUSTED ODDS RATIO	ROBUST STANDARD ERROR	P-VALUE	95% CONFIDENCE INTERVAL
INDIGENOUS	0.82	0.87	0.855	0.10-6.58
MALE	4.34	2.97	0.031	1.14-16.56
AGE (YEARS)	1.02	0.03	0.450	0.96-1.09
CHRONIC KIDNEY DISEASE	2.60	2.27	0.273	0.47-14.40
IMMUNOSUPPRESSION	11.49	8.43	0.001	2.73-48.42
LUNG DISEASE	4.52	3.76	0.070	0.96-1.09