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The epidemiology and microbiology of central venous catheter related bloodstream infections among hemodialysis patients in the Philippines: a retrospective cohort study

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Abstract

Background Despite efforts to improve the management of catheter-related bloodstream infections (CRBSI) in literature, temporary CVCs continue to be used for maintenance hemodialysis outside of acute care settings, particularly in the Philippines.

Methods We conducted a retrospective cohort study to investigate the incidence, outcomes, risk factors, and microbiological patterns of CRBSI among adult kidney disease patients undergoing hemodialysis at the Philippine General Hospital, the country's largest tertiary referral center. We included all adult patients who received a CVC for hemodialysis from January 1, 2018, to August 31, 2019, and followed them for six months to observe the occurrence of CRBSI and its outcomes.

Results Our study documented a CRBSI incidence rate of 6.72 episodes per 1000 catheter days, with a relapse rate of 5.08%, a reinfection rate of 15.74%, and a mortality rate of 6.09%. On multivariable regression analysis, we identified autoimmune disease, dialysis frequency of $>3\times$ per week, use of CVC for either blood transfusion or IV medications, renal hypoperfusion, drug-induced nephropathy, and hypertensive kidney disease as significant risk factors for CRBSI. Gram-negative bacteria, including *B. cepacia* complex, *Enterobacter*, and *Acinetobacter* spp, were the most common organisms causing CRBSI. Multidrug-resistant organisms (MDROs) comprised almost half of the isolates ($n=89$, 44.5%), with Coagulase-negative Staphylococcus species having the highest proportion among gram-positive organisms and Acinetobacter spp. among gram-negative isolates.

Conclusion Our findings emphasize the need for more stringent measures and interventions to prevent the propagation of identified pathogens, such as a review of sterile technique and adequate hygiene practices, continued surveillance, and expedited placement and utilization of long-term access for patients on maintenance hemodialysis. Furthermore, CVC use outside of hemodialysis should be discouraged, and common antibiotic regimens such as piperacillin-tazobactam and fluoroquinolones should be reviewed for their low sensitivity patterns among gram-negative isolates. Addressing these issues can improve hemodialysis patients' outcomes and reduce the CRBSI burden in our institution.

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Keywords Catheter-related Bloodstream Infection, Chronic Kidney Disease, Hemodialysis, Central Venous Catheter, Multidrug-resistant organisms

Background

Hemodialysis (HD) central venous catheters (CVCs) are responsible for half of the infections in HD patients, with catheter-related bloodstream infections (CRBSI) being the second most common cause of mortality [1–4]. Its incidence varies from 0.6 to 6.5 episodes per 1000 catheter days, depending on the definition, local policies for catheter placement and care, and duration of catheterization[1, 5–7].

In the 2019 Kidney Disease Outcomes Quality Initiatives (KDOQI) definition, CRBSI is diagnosed if all four criteria are present: 1) the presence of clinical manifestations consistent with CRBSI (fever, chills, hypotension), 2) at least one positive blood culture result from a peripheral source (dialysis circuit or vein), 3) the same organism is isolated from the catheter segment and a peripheral source blood sample and 4) no other apparent source of the bloodstream infection. A positive semi-quantitative (more than fifteen colony forming units (CFU) per catheter segment, hub, or tip) or quantitative (more than 10 [2] CFU per catheter segment) culture can define a positive blood culture. If available, the following would be supportive of the diagnosis: simultaneous quantitative cultures of blood samples with a ratio of greater than or equal to 3:1 (catheter hub or tip vs peripheral dialysis circuit or vein) and differential period of catheter culture versus peripheral blood culture positivity of two hours [8].

Risk factors for CRBSI include previous catheter-related bacteremia, left-sided internal jugular vein catheters, old age, diabetes mellitus, malnutrition, prolonged use, hypoalbuminemia, and immunosuppression [5–7, 9]. Another evolving problem is the development of multidrug-resistant organisms (MDROs) [10].

It is currently suggested to limit the use of non-cuffed, non-tunneled HD CVCs to a maximum of 2 weeks due to increased risk of infection [8]. However, this is rarely possible in LMICs due to socioeconomic and logistic constraints [10]. Refusals to accept long-term dialytic prognosis, inability to create a timely vascular access, poor vasculature suitability for fistula or graft creation and maturation failure are some of the reasons for the prevalent use of CVC among the dialysis population [2].

To our knowledge, there is a noticeable paucity of local publications about CRBSI, specifically among HD patients. This study aims to describe CRBSI incidence and outcome rates, identify associated risk factors, and present the microbiological patterns of cultures and isolates among adult kidney disease patients undergoing hemodialysis. This study also serves as a foundation for future quality improvement initiatives and provides a benchmark and performance indicator for our institution.

Methods

Study population and recruitment

We conducted a retrospective cohort study that included all adult patients inserted with a CVC for hemodialysis at the University of the Philippines—Philippine General Hospital, the country's largest referral center for tertiary care, from January 1, 2018, to August 31, 2019.

In the Philippine General Hospital, where this study was conducted, the placement of non-tunneled, non-cuffed hemodialysis CVCs can occur either in the operating room setting or at the bedside under ultrasound guidance, but always adhering to strict aseptic techniques These include thorough handwashing, the use of sterile gloves, masks, and gowns, as well as the utilization of sterile drapes and equipment. It is important to note that only the attending nephrologist has the authority to order the use of the CVC for purposes other than hemodialysis, such as infusion of medications, parenteral nutrition, or blood products. Following CVC insertion, regular assessments of the catheter site are conducted to detect any signs of infection. As per protocol, dressing changes are performed using sterile techniques after each dialysis session. Education on CVC care and awareness of potential complications is provided to both patients and caregivers. However, there is no established dialysis event surveillance program in the institution.

We included all adult (>18 years) inpatients utilizing tunneled and non-tunneled CVCs for hemodialysis. Patients under the age of 18, incomplete data sets, and CVCs placed in another institution were excluded. All included participants were monitored for occurrence of outcomes (CRBSI, relapse, reinfection, and mortality) from the date of first CVC placement until the following: use of long-term non-catheter hemodialysis access (fistula or graft), conversion to peritoneal dialysis or a transplant, mortality or up to six months after study inclusion, whichever comes first.

The sources of data included medical charts, dialysis units, and microbiological laboratory records. Clinical and demographic data (age, gender, comorbidities, baseline serum creatinine, serum albumin, frequency of dialysis) and catheter information (previous history of

catheter insertion, access type, duration of use, use outside of hemodialysis, duration of insertion to the diagnosis of CRBSI and isolate identity and sensitivity) were collected. Antibiotics were used as an initial empiric regimen (for antibiotic naïve patients), and those already on board since CRBSI diagnosis were also recorded (Table 4). In cases where CRBSI diagnosis was not already recorded, the 2019 KDOQI criteria were applied by the investigators to patient data as documented in the medical records.

Despite all study participants being dialysis patients, serum creatinine levels were considered relevant in this study. Serum creatinine, a marker of muscle mass, is a crucial indicator of nutritional status and mortality risk in dialysis patients. Higher serum creatinine levels are associated with improved survival outcomes in both conventional (thrice-weekly) and less frequent (twice-weekly) hemodialysis patients, as shown by studies examining large cohorts and adjusting for potential confounders such as demographics, comorbidities, and markers of malnutrition and inflammation. Additionally, creatinine's correlation with other nutritional indicators like serum albumin and interdialytic changes further supports its utility [11–14].

Sample size

The minimum sample size required was computed using R version 4.0.3. To ensure sufficient statistical power and significance in a Cox regression analysis, at least 623 subjects are required. This calculation is based on the desired ability to detect a hazard ratio of 1.57, considered significant in the context of Cohen's d effect size (d = 0.35), with an 80% probability of correctly identifying this effect at a 5% significance level. The sample size was also calculated considering an expected event rate of 31% for CVC-related bloodstream infections among hemodialysis patients with CVC, as reported in a study by Agrawal from 2019 [15]. Additionally, adjustments were made for multiple regression analysis to account for various clinical variables, assuming that 50% of these variables would act as confounders. The covariates were anticipated to explain approximately 20% of the variability in the outcomes (R-squared = 20%). Potential covariables identified as significant at HR = $p < 0.2$ were assessed in separate multivariable models to explore associations between risk factors and CRBSI.

Definitions

1. *Relapse*—recurrence of the CRBSI due to the *same* organism occurring during the subsequent four weeks after completion of antimicrobial therapy.
2. *Reinfection* – recurrence of the infection with a *different* microorganism occurring during the subsequent four weeks after completion of antimicrobial therapy.
3. *Infection-related mortality* – defined as a) patient died after a clinical course suggesting persistent infection, b) patient died during the phase of acute infection during the study period
4. *Renal hypoperfusion*—a state in which the kidneys receive insufficient blood flow to maintain normal function and homeostasis. This condition is identified by a combination of clinical, laboratory, and imaging findings, including: a) Clinical—Symptoms of reduced kidney function such as oliguria (urine output < 400 mL/day) or anuria (urine output < 100 mL/day) or signs of systemic hypoperfusion such as hypotension (systolic blood pressure < 90 mmHg), tachycardia, and signs of shock; b) Laboratory—Elevated serum creatinine levels indicating acute kidney injury, with an increase of at least 0.3 mg/dL within 48 h or a 50% increase from baseline within 7 days or Increased blood urea nitrogen (BUN) to creatinine ratio (≥ 20:1), or Fractional excretion of sodium (FENa) < 1% and c) Imaging—Doppler ultrasound showing reduced renal blood flow or Evidence of systemic hypoperfusion on echocardiography or other relevant imaging modalities. Renal hypoperfusion will be diagnosed if the patient exhibits at least two of the above criteria in the context of a clinical scenario suggestive of reduced renal blood flow, such as dehydration, heart failure, or sepsis.

Outcome

The clinical, catheter, and demographic profiles of adult kidney disease patients undergoing hemodialysis in the Philippine General Hospital were summarized by descriptive statistics. Numerical variables were presented as median and interquartile range because of non-normal distribution, as assessed by the Shapiro–Wilk test of normality. Categorical variables were presented as absolute or relative frequencies. The patients were grouped into with or without CRBSI. The groups were compared on the different clinical, catheter, and demographic characteristics using the Mann–Whitney U test for the numerical variables and the Chi-square or Fisher exact test of homogeneity for the categorical variables, as appropriate.

The incidence of CRBSI among adult kidney disease patients undergoing hemodialysis was presented as several events per 1,000 patient-catheter days. The time-at-risk utilized was the time, in days, from catheter insertion to the day of noting CRBSI (day of blood extraction of the culture-positive blood specimen) for those who had the event, i.e., CRBSI. In contrast, for those who did not have

the event, it was the time, in days, from catheter insertion to the day of catheter removal. The incidence of CRBSI was calculated for the first CRBSI episode; subsequent catheter insertions in the same patient were recorded as either reinfection or relapse. Reinfection, relapse, and infection-related mortality rates were all expressed in percent. Catheter-specific rates were presented as CRBSI events per 1000 patient-catheter days for each catheter type.

Using Cox proportional hazards regression, survival analysis was done to determine the association of the different clinical, catheter, and demographic characteristics of the patients with developing CRBSI. Cox regression analysis determines the hazard ratio (HR), which can be used to determine the percentage increase or decrease due to the factor using the formula: $(HR—1)\times 100$. The time-to-event used was as described above. Univariable regression was initially performed to screen for risk factors, and those with p-value < 0.20 were included in the multivariable analysis. Factors with p-value < 0.05 in the multivariable regression were considered significant risk factors for CRBSI. Additionally, a standardized mean difference (SMD) was used to compare means of a covariate between groups while accounting for data variability.

SMD is used when determining the balance of covariates before and after controlling for confounders in observational studies. If SMD is below 0.2, there is a trivial difference, while if it's greater than or equal to 0.2 but less than 0.5 that means there's a small difference and if it is greater than or equal to 0.5 and less than < 0.8 then this shows moderate difference; however if the figure is greater than or equal to 0.8 it indicates large difference between two groups being compared.

The concept of this study defined HR as the rate at which one variable may change when all other variables are held constant such that they would not affect the measures taken by researchers for evaluation purposes. Given this, the paper directs that all other factors are held constant and that covariates with an SMD < 0.02 are comparable across groups. This lowers the impact of variability on HR. With this, the analysis guarantees that covariates incorporated into calculation of the adjusted HR had no significant bias towards any group because both groups have similar characteristics of these variables making the HR more accurate and reliable.

Results

Clinical demographics

Eight hundred and thirty-two patients were screened at the start of the study. Ninety-five patients were excluded due to CVC insertion outside of our institution. A total of seven hundred seven patients were included in the final analysis. One hundred ninety-seven patients were classified with CRBSI, while five hundred ten participants were classified as without CRBSI. (Fig. 1). Table 1 presents the demographics of the study population. The median age of participants was similar in both groups at 54 years old, with males comprising most of the population.

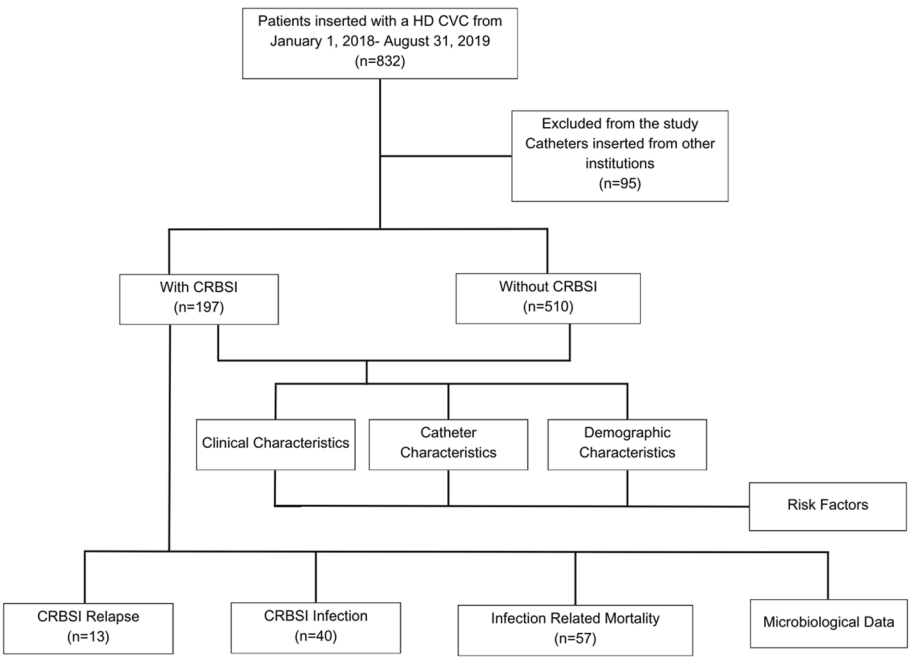

Fig. 1 Flow diagram of the study

Table 1 Baseline characteristics of patients

Patient characteristics	Total *n* = 707	With CRBSI *n* = 197	Without CRBSI *n* = 510	*P* value
Age	54.00 (20.00)	54 (20)	53 (22)	0.959
Sex				0.219
Male	401 (56.71%)	119 (60.41%)	282 (55.29%)	
Female	306 (43.29%)	78 (39.59%)	228 (44.71%)	
Comorbidities				
Hypertension	319 (45.12%)	118 (59.90%)	201 (39.41%)	< 0.001
Diabetes Mellitus	194 (27.44%)	68 (34.52%)	126 (24.71%)	0.009
Cardiac Disease	84 (11.88%)	36 (18.27%)	48 (9.41%)	0.001
Neurologic Disease	51 (7.21%)	19 (9.64%)	32 (6.27%)	0.120
Malignancy	101 (14.28%)	22 (11.17%)	79 (15.49%)	0.141
Autoimmune Disease	28 (3.96%)	13 (6.60%)	15 (2.94%)	0.025
No comorbidity	177 (25.04%)	26 (13.20%)	151 (29.61%)	< 0.001
Laboratory Data				
Baseline Creatinine (mg/dL)		8.02 (5.55)	2.675 (3.97)	0.312
Serum Albumin (g/dL)		3.0 (0.90)	3.2 (0.90)	0.014
Hemodialysis Data				
Prior central venous catheterization	23 (3.25%)	20 (10.15%)	3 (0.59%)	< 0.001
Catheter type				0.330
Non-tunneled	695 (98.30%)	192 (97.46%)	503 (98.63%)	
Tunneled	12 (1.70%)	5 (2.54%)	7 (1.37%)	
Access Site				
Internal jugular	663 (93.80%)	173 (87.82%)	490 (96.08%)	< 0.001
Subclavian	12 (1.70%)	5 (2.54%)	7 (1.37%)	0.330
Femoral	32 (4.52%)	19 (9.64%)	13 (2.55%)	< 0.001
Access Laterality				0.018
Left	12 (1.70%)	7 (3.55%)	5 (0.98%)	
Right	695 (98.30%)	190 (96.45%)	505 (99.02%)	
Dialysis frequency (per week)				< 0.001
> 3x/week	119 (16.83%)	60 (30.46%)	59 (11.57%)	
≤ 3x/week	588 (83.17%)	137 (69.54%)	451 (88.43%)	
Catheter use outside of Hemodialysis				
Blood transfusion	41 (5.80%)	32 (16.24%)	9 (1.76%)	< 0.001
Intravenous medications	135 (19.09%)	103 (52.28%)	32 (6.27%)	< 0.001
Total parenteral nutrition	9 (1.27%)	3 (1.52%)	6 (1.18%)	0.715
Etiology of Kidney Disease				
Sepsis	223 (31.54%)	81 (41.12%)	142 (27.84%)	0.001
Renal Hypoperfusion	111 (15.70%)	31 (15.74%)	80 (15.69%)	0.987
Tubulointerstitial Nephritis	84 (11.88%)	10 (5.08%)	74 (14.51%)	0.001
Drug-Induced Nephropathy	80 (11.31%)	30 (15.23%)	50 (9.80%)	0.041
Obstructive Uropathy	103 (14.57%)	22 (11.17%)	81 (15.88%)	0.111
Diabetic kidney disease	179 (25.32%)	63 (31.98%)	116 (22.75%)	0.011
Hypertensive kidney disease	213 (30.13%)	101 (51.27%)	112 (21.96%)	< 0.001
Glomerulonephritis	136 (19.23%)	41 (20.81%)	95 (18.63%)	0.509
Cardio-renal syndrome	77 (10.89%)	33 (16.75%)	44 (8.63%)	0.002
Polycystic Kidney Disease	12 (1.70%)	1 (0.51%)	11 (2.16%)	0.128

Abbreviations: *CRBSI* Catheter Related Blood Stream Infection

Hypertension was the most common comorbidity in both groups, followed by diabetes mellitus and cardiac disease (Table 2). The majority utilized right-sided, non-tunneled, internal jugular access. Most participants in both groups also received hemodialysis less than or equal to three times per week.

Patients with CRBSI also had more previous CVC inserted at 10.15% than those without at 0.59%. However, this difference may be due to the sample size discrepancy wherein there were only 3 without CRBSI but 20 for the group with CRBSI.

Patients with CRBSI also had more frequent use of their CVCs for purposes other than hemodialysis, with intravenous medications being the most commonly infused substances through the third lumen of the catheter. Hypertensive kidney disease, sepsis-associated nephropathy, and diabetes kidney disease were the most common etiologies of renal failure in both groups.

Table 2 Factors Associated with Catheter-related Blood Stream Infections

Factors	Univariable			Multivariable		
	HR	*95% CI*	*P value*	*Adj. HR*	*95% CI*	*P value*
Age	1.00	0.99, 1.01	0.394			
Female Sex	0.73	0.55, 0.98	0.038	0.85	0.61, 1.19	0.351
Comorbidities						
Hypertension	1.29	0.96, 1.72	0.092	0.86	0.52, 1.41	0.545
Diabetes Mellitus	0.97	0.71, 1.31	0.823			
Cardiac Disease	1.35	0.93, 1.95	0.113	0.98	0.66, 1.46	0.919
Neurologic Disease	1.62	1.01, 2.61	0.046	0.94	0.56, 1.58	0.818
Cancer	1.02	0.65, 1.60	0.922			
Autoimmune Disease	2.18	1.24, 3.83	0.007	2.71	1.41, 5.20	0.003
Laboratory Data						
Baseline Creatinine (mg/dL)	1.03	1.00, 1.06	0.090	1.03	1.01, 1.06	0.015
Serum Albumin (g/dL)	0.67	0.53, 0.85	0.001	0.72	0.56, 0.92	0.009
Hemodialysis Data						
Prior central venous catheterization	1.33	0.78, 2.24	0.293			
Tunneled catheter	0.20	0.06, 0.64	0.007	0.50	0.15, 1.63	0.249
Right-sided access	0.29	0.13, 0.61	0.001	0.25	0.11, 0.55	0.001
Dialysis > 3x/week	4.65	3.39, 6.39	< 0.001	2.45	1.71, 3.49	< 0.001
Use outside HD						
Blood transfusion	3.81	2.56, 5.66	< 0.001	1.63	1.04, 2.55	0.032
IV medications	6.83	5.10, 9.15	< 0.001	3.49	2.47, 4.93	< 0.001
Total parenteral nutrition (TPN)	1.80	0.57, 5.63	0.316			
Access Site						
Femoral	2.30	1.60, 3.30	< 0.001	2.40	1.66, 3.50	< 0.001
Jugular	1.10	0.75, 1.61	0.090	1.12	0.76, 1.63	0.564
Subclavian	0.80	0.55, 1.15	0.225			
Etiology of Kidney Disease						
Sepsis	3.18	2.35, 4.31	< 0.001			
Renal Hypoperfusion	2.11	1.41, 3.17	0.001	1.63	1.05, 2.53	0.028
Tubulointerstitial Nephritis	1.17	0.61, 2.25	0.639			
Drug-Induced Nephropathy	3.55	2.34, 5.37	< 0.001	2.50	1.60, 3.93	< 0.001
Obstructive Uropathy	0.84	0.53, 1.31	0.431			
Diabetic kidney disease	0.90	0.65, 1.23	0.495			
Hypertensive kidney disease	1.64	1.22, 2.20	0.001	2.22	1.32, 3.73	0.003
Glomerulonephritis	0.89	0.63, 1.25	0.498			
Cardio-renal syndrome	1.27	0.87, 1.86	0.216			
Polycystic Kidney Disease	0.29	0.04, 2.07	0.217			

Incidence rates and outcomes of CRBSI

One hundred ninety-seven episodes of CRBSI were recorded during the observation period. A total of forty-one patients experienced multiple CRBSI events, ten of whom experienced a relapse, while thirty-one had a reinfection episode. The median duration of catheter placement was 21 days among patients who developed CRBSI, compared to 17 days among those who did not develop CRBSI.

Overall, the CRBSI incidence rate was documented at 6.72 episodes per 1000 catheter days, with a relapse rate of 5.08%, reinfection rate of 15.74%, and mortality rate of 6.09%. By location, femoral catheters showed significantly higher incidence rates, with 15.04 episodes. This was followed by internal jugular catheters (6.5 CRBSI), while subclavian catheter use had the lowest infection rate, at 3.52 cases per 10,000 person-catheter days. This finding is consistent with previous research that indicated fewer complications using the subclavian site compared to other sites. In particular, there were significantly lower incidences of major catheter-related complications such as catheter-related bloodstream infections and symptomatic deep vein thrombosis for subclavian as compared to jugular and femoral sites. Wherein, the reported incidence rate of 1.5 per 1000 catheter days for subclavian catheters were lower compared to jugular and femoral sites [16].

The non-tunneled catheter had a higher incidence rate of 6.91 than the tunneled catheter of 3.52 CRBSI per 1000 person-catheter days. Meanwhile, based on laterality, CRBSI was found to be more frequent with a left-sided placement (21.88 episodes) than a right-sided placement (6.56 episodes per thousand catheter days). The high incidence of left-sided placement may be driven by the fact that right sided placement was not always feasible. In some cases, anatomical or pathological factors such as thrombosis, vascular stenosis or prior surgical interventions could have prevented placing the catheter on the right side of the body. For example, in situations with cannulation difficulties or reduced vascular access, it may be necessary to use the left internal jugular vein. The high risk of infection from left-sided placements could probably also be linked to these root issues which could compromise sterility and efficacy of catheter insertion altogether.

Figure 2 illustrates the Kaplan–Meier infection-free survival curve of developing CRBSI among patients undergoing hemodialysis using a CVC with a median infection-free survival time.

Risk factor analysis

Adjustments were made based on their significance in univariable analyses ($p < 0.2$) to control for potential confounders and provide a more accurate assessment of the factors associated with CRBSI.

Based on this, demographic variables such as age and sex were included. Several comorbidities, including hypertension, cardiac disease, neurologic disease, and

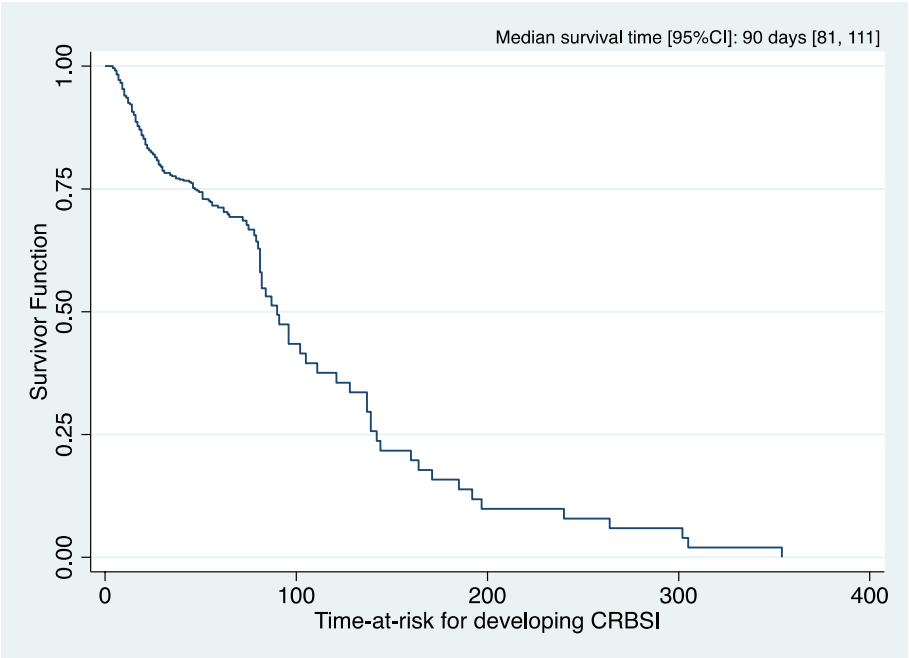

Fig. 2 Survival curve of developing CRBSI among adult kidney disease patients undergoing hemodialysis

autoimmune disease, were also considered. Laboratory data adjustments included baseline creatinine levels and serum albumin levels. Hemodialysis-related factors, such as the use of a tunneled catheter, right-sided access, and the frequency of dialysis (more than three times per week), were also accounted for.

The analysis also adjusted for blood transfusions and intravenous medications. Lastly, the etiology of kidney disease, specifically renal hypoperfusion, drug-induced nephropathy, and hypertensive kidney disease, were included as covariates. For the adjusted HR, a standardized mean difference of less than 0.2 was taken to indicate a negligible difference in the mean or prevalence of a covariate in the risk factor.

Table 2 demonstrates the multivariable analysis of risk factors for CRBSI. The presence of autoimmune disease ($p=0.003$), dialysis frequency of more than three times per week ($p<0.001$), use of CVC for either blood transfusion ($p=0.032$) or IV medications ($p<0.001$), renal hypoperfusion ($p=0.028$), drug-induced nephropathy ($p<0.001$) and hypertensive kidney disease ($p=0.003$) were all significantly associated with CRBSI development.

Every 1 mg/dL increase in baseline serum creatinine also increased the hazard of developing CRBSI by 3%. This was determined by calculating the percentage increase using the hazard ratio (HR) 1.03 with the formula: percentage increase $(1–1.03)\times100$. On the other hand, a right-sided access placement was associated with a reduced risk for CRBSI ($p=0.001$) and serum albumin ($p=0.009$). For every 1 g/dL increase in serum albumin, there is a 28% decrease in the risk of developing CRBSI.

Microbiological isolates and antimicrobial susceptibility patterns

A total of 200 organisms were isolated, with the majority being monomicrobial (94.92%). The most common organisms were gram-negative bacteria (52%), with *Burkholderia cepacia* complex (13%), *Enterobacter* spp (13%), and *Acinetobacter* (11%) being the predominant isolates. Gram-positive organisms were led by Coagulase-negative *staphylococci* (CONS) (34.5%) and *Staphylococcus aureus* (13%)—fungal species comprised around 2% of the isolates. Detailed data on antimicrobial susceptibility patterns and treatment are available in the supplementary materials (Table 5).

Supplementary data

The supplementary materials provide microbiological isolates, antimicrobial susceptibility patterns, and detailed information on antibiotics utilized.

Discussion

CRBSI incidence varies significantly with different socioeconomic backgrounds, typically demonstrating lower incidence rates in high income countries (or HICs) compared to low income countries (LICs) and lower middle income countries (LMICs). Generally, incidence rates exceeding 2 episodes per 1000 catheter days indicate room for improvement [17, 18]. Our study set in a public institution serving indigent patients found an overall CRBSI incidence rate of 6.72 CRBSI episodes per 1000 catheter days. While this is higher than in HICs, [18–22] The observed rate is still lower than those reported in other LICs and LMICs [2, 21–26]. This observed disparity in CRBSI rates can be attributed to differences in healthcare infrastructure and patient management practices. Upper middle income countries (UMICs) and HICs benefit from healthcare systems with well-equipped facilities, advanced medical technologies, and a highly skilled workforce [20]. These resources enable infection control measures to be rigorously implemented across clinical settings [27, 28]. These include protocols for the insertion, maintenance, and timely removal of catheters, coupled with regular surveillance to promptly detect and manage infections like CRBSI. Furthermore, patients generally experience better access to preventive healthcare services and effective chronic disease management programs [21, 29]. Conversely, LMICs such as the Philippines face substantial challenges, including limited healthcare resources, inadequate infrastructure, and variable adherence to infection control protocols [2, 24, 26]. These constraints contribute to heightened burdens of infectious diseases and healthcare-associated infections, such as CRBSI.

Several factors in our cohort contributed to CRBSI formation in our cohort, including frequent use of dialysis access outside of hemodialysis, extensive non-tunneled catheter usage, and prolonged catheter placement (median duration = 21 days), all of which have been noted in the literature to promote CRBSI formation [1, 20, 30]. Notably, specific catheter characteristics such as left-sided (21.88 episodes per 1000 catheter days), non-tunneled (6.91 episodes per 1000 catheter days), and femoral access (15.04 episodes per 1000 catheter days) correlate with higher infection rates, consistent with existing literature [20, 26, 31–35].

The reasons why left-sided catheter placements pose a greater infection risk compared to right-sided catheters are not fully understood, but anatomical and procedural factors are believed to play significant roles. The longer and more tortuous path of a left-sided catheter can increase the risk of blood flow stasis and thrombus formation, which can serve as a nidus for infection. Additionally, the technical challenges associated with

inserting a left-sided catheter often lead to more manipulation and adjustments, increasing the risk of pathogen introduction [31].

On the other hand, non-tunneled catheters lack the protective tunneling under the skin that tunneled catheters have. This absence exposes the catheter directly to skin flora and environmental pathogens during insertion and while in place [36]. Non-tunneled catheters typically have shorter dwell times, contributing to their higher infection rates as they are more frequently replaced, creating repeated opportunities for contamination and infection [37, 38].

Using the femoral vein as an access site for catheter placement is relatively common in clinical practice, especially in situations where immediate vascular access is required, such as in critically ill patients or those with difficult peripheral venous access [39, 40]. However, this approach is associated with a higher risk of CRBSI than other access sites like the subclavian vein [31, 41]. This is because the femoral region is anatomically closer to the groin, which harbors a higher density of skin flora bacteria. This proximity increases the likelihood of contamination during catheter insertion and maintenance if strict aseptic techniques are not adhered to.

In contrast, subclavian vein access is often preferred over femoral access due to its lower infection risk, as its location away from high concentrations of skin flora reduces contamination during catheter insertion. Additionally, the subclavian vein allows for easier securing of the catheter, minimizing accidental dislodgement and further lowering infection rates [41].

The multivariable analysis reaffirms known risk factors for CRBSI, including an immunocompromised state, frequent hemodialysis, CVC manipulation outside of hemodialysis, and elevated creatinine levels [3, 4, 20, 30, 42]. Conversely, right-sided CVC placement and elevated serum albumin levels decrease CRBSI risk. Infusion-related factors such as blood products and IV medication infusion (but not parenteral nutrition) significantly influence CRBSI development, consistent with published studies. [33].

Although primarily intended for hemodialysis access, CVC can also be employed for various medical procedures such as blood transfusions, intravenous (IV) medication administration, or parenteral nutrition. The prolonged use of CVCs for these purposes extends their dwell time, which is consistently linked to heightened colonization by pathogenic microorganisms and subsequent bloodstream infections like CRBSI. Furthermore, the versatility of CVCs in medical settings outside of hemodialysis necessitates frequent manipulation, such as for medication infusions or blood product administration [43]. Each manipulation event presents an opportunity for microbial contamination, increasing the likelihood of infection. Studies underscore that such manipulations contribute significantly to the overall infection risk associated with these catheters [44]. Hence, in clinical settings, using CVCs for non-dialysis should ideally be minimized to reduce the risk of complications such as CRBSI.

In the locale of the study, efforts are made to adhere to strict aseptic techniques during the placement and maintenance of hemodialysis CVCs. These protocols include rigorous handwashing, sterile gloves, masks, gowns, sterile draping, and regular assessments of catheter sites for signs of infection. Education programs ensure that both patients and healthcare providers are well-informed about proper CVC care and potential complications. Importantly, only attending nephrologists are authorized to order CVC use for purposes beyond hemodialysis, such as medication infusion or parenteral nutrition, to minimize the risk of infection. Despite these precautions, our cohort revealed that a substantial proportion of dialysis catheter access was utilized for purposes other than hemodialysis, including blood transfusions, intravenous medications, and total parenteral nutrition. Although a dedicated port is used for these infusions, its use still carries a risk of infection. This suggests that other underlying issues could contribute to the development of infections, highlighting the need for further investigation into these contributing factors [45, 46].

Another distinctive finding in the results was the predominance of gram-negative rods as the main causative agent of CRBSI, accounting for 52% of the cases, significantly higher than gram-positive bacteria at 48%. While gram-positive bacteria historically predominated in CRBSI among hemodialysis patients, [2, 18, 21, 47, 48] an evolving trend towards gram-negative organisms has been noted globally [9, 15, 49, 50]. Notably, *Enterobacter* spp., *B. cepacia* complex, and *Acinetobacter* spp. Constitute a substantial portion of gram-negative isolates in our cohort.

Multidrug-resistant organisms (MDROs) comprised an alarming proportion of isolates ($n=89$, 44.5%), with *Acinetobacter* species encompassing the most common MDROs based on the results (Supplemental Table 5). Consequently, we also found resistance to aminoglycosides, fluoroquinolones, and piperacillin-tazobactam in gram-negative isolates.

Several factors may have contributed to this shift towards gram-negative rod predominance. Increased use of broad-spectrum antibiotics, such as carbapenems and glycopeptides (Supplemental Table 4), could lead to the selection of resistant gram-negative pathogens (Supplemental Table 3) [51, 52]. Prolonged catheter duration provides a longer timeframe for bacteria to colonize and

form biofilms, which are particularly resilient against antibiotics. This increases the likelihood of gram-negative rod infections, as these pathogens can thrive in the biofilm environment and are often resistant to many antibiotics [53–55].

Frequent catheter utilization outside of hemodialysis, extensive non-tunneled catheter usage, and prolonged catheter placement have all been noted as risk factors for CRBSI formation. These practices can increase exposure to a broader range of environmental and opportunistic gram-negative bacteria. For instance, *Enterobacter* spp. and *Acinetobacter* spp. are common in hospitals and can easily colonize catheters used for extended periods.

Exploring the relationship between gram negative rods and these risk factors, we found that the combination of prolonged catheter use, and specific antibiotics used in our setting may be selected for gram-negative pathogens. Frequent catheter manipulations and the immunocompromised state of many patients further increase susceptibility to infections caused by GNRs. This highlights the need for targeted infection control strategies and the careful selection of empirical antibiotic therapies to address the specific risks associated with gram negative rods in the population [15, 49, 50].

A fifth of our CRBSI cohort experienced disease recurrence ($n=41$, 20.81%) with mostly a different organism (reinfection rate = 15.74% vs relapse rate = 5.08%), a finding comparable to the experience of Shahar et al. and Mokrzycki et al. who noted recurrence rates of 9—31% in their HD cohorts [21, 56]. This observation suggests that while a significant proportion of patients experienced a recurrence of CRBSI, most were due to new infections rather than relapses. This finding underscores the persistent risk of acquiring new infections despite previous treatment, which could be attributed to ongoing exposure to healthcare settings and interventions, as noted in similar studies by Shahar et al. and Mokrzycki et al. [15, 56, 57]. We also documented a mortality rate of 6.09%, at par with previously reported attributable mortality to CRBSI, ranging from 4–8% [18, 20, 58, 59]. Factors contributing to this include a high incidence rate leading to a high event rate, the presence of MDROs, and comorbidities in the population (41% of CRBSI with sepsis).

Lastly, results showed that some of our empiric antibiotic regimens, such as piperacillintazobactam and levofloxacin, exhibited low sensitivity patterns among our isolates, as detailed in (Supplemental Table 6). Empiric antibiotic therapy forms the cornerstone of initial treatment protocols for CRBSI, aimed at promptly addressing infections pending definitive microbiological identification [59]. The observed low sensitivity of piperacillin-tazobactam and levofloxacin suggests potential limitations in their efficacy as first-line therapeutic options in our patient population. This observation is particularly significant as these antibiotics are commonly utilized in clinical settings due to their broad-spectrum coverage and presumed effectiveness against gram-negative organisms frequently implicated in CRBSI [60].

In comparing our findings with past literature, particularly considering the healthcare situation in the Philippines, several differences and contextual factors emerge. For instance, a study by Mantaring et al. reported a lower overall CRBSI incidence of 2.63 per 1,000 catheter days among hemodialysis patients compared to our higher incidence rates [61]. This discrepancy may be attributed to differences in healthcare settings, patient demographics, and catheter management practices. Mantaring et al. also highlighted that extensive use of non-tunneled CVCs had a higher CRBSI rate, aligning with our findings that long-term non-tunneled catheter usage contributes significantly to CRBSI formation [61, 62]. Moreover, local studies with CRBSI have noted hypertension as the most common comorbidity and identified *E. coli* and *Staphylococcus aureus* as predominant pathogens [63, 64]. Our study similarly identifies hypertension as a frequent comorbidity but finds a notable shift toward gram-negative organisms, particularly *Enterobacter spp., B. cepacia* complex, and *Acinetobacter* spp. This shift may be linked to local antibiotic usage patterns and prolonged catheter durations, which can foster the proliferation of gram-negative bacteria [65, 66]. Additionally, it was emphasized that using multiple accesses, higher blood sugar levels, and low serum sodium levels increased healthcare-associated infections (HCAIs) in end-stage renal disease patients [67, 68]. Our findings also indicate that elevated creatinine levels and frequent catheter manipulation are significant risk factors for CRBSI, suggesting a need for targeted preventive strategies in the local context [63, 64].

Strength and limitations

To our knowledge, this is the first local study to identify CRBSI rates, risk factors, and outcomes and provide a sensitivity analysis of microbial growth utilizing the 2019 KDOQI CRBSI criteria.

The study has several limitations. First, it was a single-center study, and the retrospective nature of our study increased the risk of confounders. Second, we did not include exit site infection rates, which may be a risk factor for CRBSI. Third, the study did not account for hygiene and dialysis practices by the hospital staff. This includes accounting for the presence or absence of an infection control program, dialysis event surveillance program, and whether a formal CVC insertion bundle—which defines a standardized set of protocols for catheter insertion and maintenance— was systematically

applied and followed in the hospital setting. Due to this limitation, the possibility of poor compliance with standard hygiene and limitations in healthcare programs was an unknown risk factor. Surrogates for hygiene, such as educational background and financial status, may be utilized and considered in future studies. Moreover, programs involving monitoring and surveillance of dialysis patients can be accounted for in future studies.

Fourth, the Infectious Disease Society of America (IDSA) criteria of 2009 were not used for diagnosis in the study. IDSA is the most commonly used criteria for diagnosing CRBSI among dialytic patients. In the IDSA guidance, the mainstay in diagnosing CRBSI is positive blood cultures from the peripheral veins and catheter hub that must all meet the quantitative or differential time to positivity (DTP) criteria [41]. However, implementing the IDSA criteria is controversial due to the difficulty in obtaining a culture from a peripheral vein in HD patients because of exhausted vascular access and lack of validation for the dialytic population. In a study by Quittnatt et al., a combination of venous catheter hubs and HD circuits was reported to be the most sensitive and accurate way to diagnose CRBSI compared to peripheral venipunctures [41]. With this in mind, we opted to use the 2019 Kidney Disease Outcomes Quality Initiative (KDOQI) CRBSI case definition, which incorporates both the Centers for Disease Control (CDC) and IDSA case definitions [65].

Fifth, the difference between cuffed and uncuffed CVCs and its impact was not explored. This was due to data limitations as majority of the patients observed was noncuffed as set by the practice at the locale of the study. Lastly, given the distinct microbiological epidemiology of bacterial isolates and the observed incidence of CRBSI in this study, it is important to recognize the regional specificity of these findings. The generalizability of the results to settings different from our clinical environment may be limited.

Lastly, our study did not differentiate between Acute Kidney Injury (AKI) and End Stage Kidney Disease (ESKD) patients. This distinction is significant because AKI and ESKD patients have different clinical profiles: AKI typically involves sudden onset and temporary catheter use, while ESKD often necessitates prolonged catheter exposure. These differences could influence both the risk factors for CRBSI and the clinical outcomes, as AKI patients may have varying recovery trajectories compared to the more stable but chronically ill ESKD patients. Not accounting for these distinctions may limit the study's ability to fully capture the nuances in CRBSI risk and outcomes across these patient groups.

Conclusions

This study highlights the incidence and catheter-specific rates of central line-associated bloodstream infections (CRBSIs) in our hemodialysis cohort and identifies modifiable risk factors that impact our rates. Our findings suggest a concerning predominance of gram-negative and multidrug-resistant organisms among bacterial isolates, emphasizing the need for more stringent measures and interventions, continued surveillance, expedited placement, and long-term access for patients on maintenance hemodialysis. Moreover, CVC use outside of hemodialysis should be discouraged. We also observed low sensitivity patterns among gram-negative isolates for commonly used antibiotics such as piperacillin-tazobactam and fluoroquinolones, highlighting the importance of balancing antimicrobial stewardship and adequate coverage when selecting antibiotic regimens. Addressing these issues can prevent the propagation of identified pathogens and improve outcomes for our hemodialysis patients.

Abbreviations

CRBSI	Catheter-Related Bloodstream Infection
CVC	Central Venous Catheter
MDRO	Multidrug Resistant Organism
DTP	Differential Time to Positivity
IDSA	Infectious Disease Society of America
KDOQI	Kidney Disease Outcomes Quality Initiative
CFU	Colony Forming Units
CONS	Coagulase Negative Staphylococcus
CDC	Center for Disease Control
TPN	Total Parenteral Nutrition

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Renz Michael Pasilan and Isabelle Dominique Tomacruz-Amante designed the study, collected and analyzed the data, and wrote the manuscript. Coralie Therese Dimacali contributed to the study design, data collection, and manuscript preparation.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the University of the Philippines Manila Research Ethics Board (UPM-REB, code 2021–153-01). All methods described in this manuscript were carried out in accordance with relevant guidelines and regulations, including the Declaration of Helsinki for research involving human

participants, human material, or human data. The waiver for informed consent was also granted by the University of the Philippines Manila Research Ethics Board as our retrospective study involved the use of pre-existing data that were analyzed anonymously.

Consent for publication
Not applicable. This manuscript does not contain any identifying images or information.

Competing interests
The authors declare no competing interests.

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