RESEARCH ARTICLE

Analysis of survival for patients in relation to central venous catheter and nosocomial blood stream infections: A case study of Aga Khan University Hospital, Nairobi [version 1; peer review: 1 approved, 1 not approved]

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Abstract

Background: This study was focussed on survival rates of patients admitted to acute care units who utilized medical devices known as central venous catheters (CVC). CVCs are useful devices in clinical care; however some infections such as central line associated bloodstream infections (CLABSI) may occur, which are associated with increased lengths of stay and costs as well as higher morbidity and mortality rates.

The overall objective of the present study was to determine survival probabilities and hazard rates for patients who used CVC devices and compare the subgroups by infection status.

Methods: The study was focused on all patients who were admitted to Critical Care Units between 8th December 2012 and 31st March 2016 and utilized CVC devices. It was a retrospective study. Survival analysis techniques, test of equality of proportions, Man-Whitney test and Chi-square test of independence were used.

Results: A total of 363 out of 1089 patients included in the study died during hospitalization. 47 patients developed nosocomial CLABSI. The average duration was 18.19 days and median of 12 days for hospitalized patients who did not develop a nosocomial CLABSI compared to an average of 56.79 days and a median of 51 days for those who did. There was a significantly higher proportion of mortality of those who developed nosocomial CLABSI compared to those that didn't (p-value=0.01379). The results indicate that there was a significant association between infection status and discharge status, and significant difference to the survival rates of the patients based on infection status.

Conclusions: There is a significant impact on mortality and morbidity of patients who develop nosocomial CLABSI. The duration of hospitalization by patients who developed CLABSI was significantly

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higher compared to patients who did not. Increased length of stay leads to higher cost of hospitalization.

Keywords

Critical care unit, central venous catheter, length of stay, nosocomial infection, survival time, survival analysis, survival function, central line associated blood stream infection, CLABSI

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Introduction

Central line associated bloodstream infection (CLABSI) is a type of infection that affects patients who utilize central venous catheter (CVC) during their hospitalization. CVC refers to any central venous access device inserted into the internal jugular, subclavian or femoral vein that terminates in the inferior vena cava or right atrium¹. CVCs are commonly used in wards and critical care units, such as the intensive care unit (ICU), and they are also referred to as central lines. In accordance with The Joint Commission (2012), CVCs are essential in health care provision as they facilitate administration of medications, intravenous fluids, and hemodialysis among other functions. CVCs are used both in the in-patient and out-patient clinical care management².

According to The Joint Commission (2012), there are a variety of CVCs available in various sizes as well as different catheter materials, for example CVCs can be single or multi-lumen (double, triple or quadruple lumen). Another categorization by design classifies them as tunnelled catheters, non-tunnelled catheters, peripherally inserted central catheters and implantable ports². The choice of catheter is as a result of defined need and preferences of the clinical care giver or the patient. Every catheter device carries with it some risk of infection, however, the extent of risk depends on the type of catheter used³.

Healthcare associated infection (HAI) refers to infections that occur in the course of healthcare management in any setting, more specifically, the infections acquired during hospitalization are referred to as nosocomial infections^{2,4}. US Centers for Disease Control and Prevention (2016) observed that there was ~46% decrease in CLABSIs in hospitals across the U.S.A from year 2008 to 2013, whilst about 30,100 still occurred in critical care units and wards⁵. There was a declaration by the European Union that policy on HAI prevention be prioritized in 2008⁶.

Several studies have linked CLABSIs to prolonged hospitalization and increased health management cost, as well as increased morbidity and mortality^{2,7-12} and ¹³. Morgan *et al.* (2010) conducted a five year study, in which the authors established that HAIs, especially CLABSIs, contributed to about one third of unexpected in-hospital mortality¹³. Soufir *et al.* (1999)

conducted a prospective, matched cohort study from 1st January 1990 to 31st December 1995, in two ICUs in Paris, France and deduced that for ICU survival rates, the risk of death was significantly increased in patients with catheter related septicaemia as compared to control patients who did not develop septicaemia, with a relative risk of 2.06 (95% CI, 1.16-3.68; p-value <0.05)⁸. Garnacho-Montero *et al.* (2008) found that the median time from insertion of the catheter to the development of bacteraemia was 10 days. Further, 18 out of 66 patients died in the ICU (27.3%)¹⁰.

However, various studies face a myriad of challenges which may be attributed to difficulties in estimating the mortality resulting from blood stream infections^{8,14} and¹⁵. De Angelis *et al.* (2010) observed that when the duration of hospitalization of patients is increased, chances of utilizing invasive catheter devices increases leading to likelihood of infection¹⁴. Umscheid *et al.* (2011) observed that majority of researchers have not been able to relate CLABSIs autonomously with increase in mortality due to multiple causes of patient mortality such that exclusive impact of an infection may not be explicit¹⁶. Carrico and Ramírez (2007) observed that it may not be easy to determine the patients who die “with” CLABSI compared to those who die “because of” CLABSI¹⁵.

Very few studies have been carried out on CVC utilization or its relationship with CLABSI, in particular in developing countries. Methodologies utilised in some published studies are varied, with some facing validity problems, necessitating the need for more studies. Hospitals follow a distinct culture of patient safety programmes, which among other factors affect outcomes of hospitalized patients in different ways. Globally, the risk associated with nosocomial CLABSI is dire, and even though there has been application of various strategies to reduce the impact on patients, it remains a crucial problem.

This study was intended to provide results that explain survival for patients who used CVC devices and developed CLABSI during their duration of hospitalization and compare with those who do not develop the infection in Kenya. The conceptual framework as adopted from De Angelis *et al.*, 2010¹⁴ can be viewed in [Figure 1](#).

Figure 1. Conceptual framework.

The first state: hospital critical care admission refers to the date when patients who utilized CVC devices during hospitalization were admitted. The second state: nosocomial infection, captures the date the nosocomial CLABSI was detected. Discharge/transfer and death, refers to the date the admitted patients exited the hospital¹⁴.

Objectives

The overall aim was to determine the survival probabilities and hazard rates for patients who used CVC and establish factors affecting their survival and assess how they differ with the subset of the population that develops CLABSI. The specific objectives were as follows: i) to assess the survival probabilities for persons who utilized CVC during hospitalization; ii) to compare the survival time of patients' group with CLABSI and the group not infected; iii) to determine whether there is an association between infection status and mortality; iii) to determine whether mortality is significantly different between the two groups and to determine factors that affect survival of patients with CLABSI.

Methods

Study setting and participants

The study was conducted at critical care units of Aga Khan University Hospital, Nairobi, Kenya namely 11-bed medical-surgical ICU, 6-bed coronary care unit, 4-bed cardiothoracic intensity care unit and 16-bed high dependency unit. The focus was on acute care admitted patients, who utilized CVC access devices between 8th December, 2012 and 31st March, 2016. The data was obtained retrospectively and included the following variables: patient's age, date of admission and discharge, discharge status, count of devices utilized, type of CVC device used, gender, infection status, event status and survival time in days. Data were obtained from the hospital's electronic database and infection control surveillance datasheets. Infection control team of specialized nurses were involved in data collection. A CLABSI was considered nosocomial if a recognized pathogen was isolated from one or more percutaneous blood cultures after 48hrs of vascular catheterization and was confirmed to be unrelated to an infection from a different site. Determination of the source of infection was determined by both intensivists and microbiologists through clinical evaluation.

Analytical methods

Data were extracted and exported into MS Excel 2010 where aggregation and organization was initially carried out. Data were then exported into Statistical Package for the Social Sciences (SPSS v.24), R GUI (R-3.1.1) and Stata (SE 11.1) for further data management, cleaning and analysis. Each statistical program was utilized to run suitable analyses as per the objectives of the study as well as for attainment of desired outputs.

Measures utilized

Both exploratory and inferential analyses were utilized. Kaplan Meier curves were used to assess the survival probabilities of exposed versus un-exposed. Log rank, Breslow, Tarone- Ware, Peto and Fleming-Harrington tests helped in testing whether the survival curves between groups differed significantly. Additional statistical tests utilized were Chi-Square test of association and test of equality of proportions, as well as Man-Whitney test.

Description of measure utilized

Survival analysis is a group of statistical techniques used in analysis whereby outcome variable of interest is time taken until an event occurs. In this study the event of interest was death, which occurred among hospitalized patients who had utilized central line devices. In survival analysis time variable is referred to as survival time, in this study, the length of stay. Censoring was done when a patient did not die by the end of hospitalization, meaning he/she was either discharged alive or transferred to another facility (lost for follow-up). Censoring assumptions provided that there was independence, randomness and non-informative censoring¹⁷. In particular, right censoring was utilized.

Terminology and notation in survival analysis

Let T denote the random variable representing survival time where $T \geq 0$. The distribution of survival times is characterized by any of three functions: the survival function ($S(t)$), the probability density ($f(t)$) or the hazard function ($h(t)$). Equation (1) shows an expression of a survival function

$$S(t) = \Pr(T > t) = 1 - F(t) \quad (1)$$

The hazard function, $h(t)$, presents instantaneous rate upon which events occur, provided no such previous events. The hazard function $h(t)$ is portrayed in Equation (2), it can also be referred to as a conditional failure rate.

$$h(t) = \lim_{\Delta t \rightarrow 0} \frac{\Pr(t < T \leq t + \Delta t | T > t)}{\Delta t} = \frac{f(t)}{S(t)} \quad (2)$$

Hazard rate is used in providing information regarding conditional failures, in model identification and as a basis of expressing survival analysis math models.

Its cumulative function (Equation (3)) produces accumulated risk up to time t ,

$$H(t) = \int_0^t h(u) du \quad (3)$$

Kaplan Meier function enables approximation of survival probabilities by use of the product limit formula. Kaplan Meier product limit formula is given by Equation (4)

$$\hat{S}(t_{(j)}) = \prod_{i=1}^j \hat{\Pr}[T > t_{(i)} | T \geq t_{(i)}] \quad (4)$$

Comparison of survival curves

The Log Rank Test is used to compare two or more Kaplan Meier Curves. The test is approximately Chi-Square particularly for large samples with $G-1$ degrees of freedom (df), where G is the number of groups involved as provided in Equation (5).

$$\text{Log-rank-Statistic} = \frac{(O_i - E_i)^2}{\text{var}(O_i - E_i)} \text{ for } i=1,2 \quad (5) \leftarrow$$

Log rank is used to test the null hypothesis that there is no significant difference between two survival curves. Similarly the alternative tests to Log rank are Breslow (Wilcoxon) and the Tarone-Ware; these tests apply different weights to i^{th} failure time.

Breslow (Wilcoxon) test weights the observed minus expected score at time t_i by the number at risk n_i over all the groups at time t_i . In this test the weights subjected at the earlier failure times are higher as compared to later failure times¹⁷.

The test statistic is as shown in Equation (6)

$$\frac{\left(\sum_j w(t_i)(m_{ij} - e_{ij}) \right)^2}{\text{var} \left(\sum_j w(t_i)(m_{ij} - e_{ij}) \right)} \quad (6)$$

for $j=1, 2, I = i^{\text{th}}$ failure.

Tarone-Ware test statistic applies more weight to the early failure times by weighting the observed minus expected score at time $t(i)$ by $\sqrt{n_i}$, where n_i refers to the number at risk.

Flemington-Harrington test uses the KM survival estimates $\hat{S}(t)$ for entire data to determine its weights for the i^{th} failure time.

Different choices of values for p and q can be done. Weights are computed as shown in Equation (7) whereas the test statistic is similar to Equation (6).

$$w(t) = \hat{S}(t_{(i-1)})^p [1 - \hat{S}(t_{(i-1)})]^q \quad (7)$$

Test of equality of proportions

We consider the difference in the two proportions to be given by $d = \frac{x_1}{n_1} - \frac{x_2}{n_2}$, which is approximately normally distributed with mean zero and

$$\text{Variance } V_p(d) = \left(\frac{1}{n_1} + \frac{1}{n_2} \right) * P(1-p) \quad (8)$$

if the counts are binomially distributed with the same parameter. The null hypothesis is such that $P_1 = P_2$, the common estimate for the proportion $\bar{p} = \frac{x_1 + x_2}{n_1 + n_2}$

Chi Square test of independence is used to determine whether there is a significant association between two categorical variables. Chi square test statistic is as portrayed in Equation (9)

$$\chi^2 = \frac{\sum_i (O_i - E_i)^2}{E_i} \text{ with } (r-1)(c-1) \text{ df} \quad (9)$$

Results

A total of 1086 patients were included in the study; males 648 (59.7%). 363 patients experienced the event of interest (death). 47 patients developed nosocomial CLABSI during their hospitalization. Table 1 summarised the participant's demographics.

Table 1. Summary of study participant's demographics.

Variable	Values	Frequency	Proportion (%)
Event status	Censored	723	66.6
	Event	363	33.4
Gender	Male	648	59.7
	Female	438	40.3
Infection status	Yes	47	4.3
	No	1039	95.7

Table 2 demonstrates survival time summary statistics disaggregated by infection status. Time was measured in terms of days. The average duration of 18.19 days (standard error (s.e) 0.611) was taken by patients who did not develop a nosocomial CLABSI compared to an average of 56.79 days (s.e of 5.171) taken by those who got an infection. Median days taken by the infected group were 51 days whereas those taken by non-infected group were 12 days.

Test of association between infection status and event (discharge) status depict a $\chi^2=6.868$, p-value=0.009, which is significant at 5% level; therefore, there is a significant statistical association between the infection status and the event (discharge) status. Test of association between gender and event (discharge) status depict a $\chi^2=0.705$, p-value=0.401, which is not significant at 5% level; hence there is no significant association between the gender of the patient and the discharge (event) status at 5% level (**Table 3**). Test of association between the gender of the patient and the infection status depict a $\chi^2=1.446$, p-value=0.229,

which is not significant at 5% level; hence there is no significant association between the patient's gender and the infection status at 5% level (**Table 3**).

Test of equality of proportions of death between CLABSI infected and group not infected by CLABSI produced a $P_1=0.511$ and $P_2=0.326$ with $\chi^2=6.0647$, p-value=0.014, the 95% CI [0.02752, 0.34121]. This indicates that the proportions between the two groups are significantly different at 5% level. Hence, nosocomial CLABSI subjects a patient to a higher mortality rate as compared to a patient who does not get the infection during hospitalization.

Survival probabilities were assessed graphically as well by use of survival tables. Graphic assessment was done by use of Kaplan Meier (KM) curves for all subjects (see **Figure 2**), in the initial period of about 50 days after admission, survival probabilities decline at relatively more close ranges as compared to the period after 50 days. The overall mean time estimate was

Table 2. Summary statistics by infection status.

Infection status	Length of stay						
	Mean	N	Std. Deviation	Std. Error of Mean	Median	Minimum	Maximum
No	18.19	1039	19.701	.611	12.00	3	202
Yes	56.79	47	35.450	5.171	51.00	6	149
Total	19.86	1086	22.054	.669	12.00	3	202

Table 3. Chi square tests of association. df, degrees of freedom.

Test	χ^2	Df	p-value
Discharge and infection status	6.868	1	0.009
Gender of the patient and discharge status	0.705	1	0.405
Gender of the patient and infection status	1.446	1	0.229

Figure 2. Survival probabilities for all patients who used central venous catheters (CVC) and by infection status.

70.72 days (95% CI; 60.362, 81.084) and the overall median time estimate was 44 days (95% CI; 36.49, 51.51). Further, graphical analysis by use of the KM curves was done for each group (infected vs not infected). As shown in [Figure 3](#), the initial stages indicate higher probabilities of survival among the patients with CLABSI as compared to the group of patients with no CLABSI. However, this trend changes after about 113 days where the survival probabilities of the group not infected are higher. At about 140 days of admission, the survival probabilities of infected group decline sharply. The small sample of the patients with nosocomial CLABSI compared to the rest (with no CLABSI) may have contributed to this pattern. The median number of days estimates for the group which did not have nosocomial CLABSI were 43 days (95% CI; 34.911, 51.089) whereas for the group whose patients developed nosocomial CLABSI was 76 days (95% CI; 36.836, 115.164) (see [Figure 2](#)). On the other hand, the average number of days estimates were 76.376 days (95% CI; 63.610, 89.141) and 83.807 days (95% CI; 67.382, 100.232) for non-infected and infected groups respectively.

Tests on the survival curves [Figure 2](#) were Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon), Tarone-Ware, Peto and Fleming-Harrington. Results from all the five tests show that the survival curves are significantly different at 5% level as provided in [Table 4](#).

Test on survival time in relation to the infection status was conducted using a two sample Wilcoxon rank sum test

(Mann-Whitney test) which is a distribution free/non parametric method. The value of test statistic was 6112.5 and a corresponding p-value $< 2.2e-16$, which indicates that it is highly significant at 5% level. We can hence deduce that there is a significant difference between the length of stay by the patients who develop nosocomial CLABSI compared to the patients who do not develop the infection. Thus the patients who develop nosocomial CLABSI stay longer in hospital.

Stratification by gender yielded the following survival curves for male and female, portrayed in [Figure 3](#). The survival probabilities for the female subgroup were higher at the initial phase of about 40 days after admission after which the male's survival rates remained higher until the end. The overall average duration by male patients was 73.69 days (95% CI; 60.970, 86.958), whereas that of female patients was 59.9 (95% CI; 60.970, 86.958). The average duration taken by the male patients who were infected by CLABSI was 94.324 days (95% CI; 73.6, 115.0), whereas that of female patients was 59.904 days (95% CI; 48.7, 71.1). Median was 46 days (95% CI; 34.8, 57.2) for male patients and 42 days (95% CI; 33.5, 50.5) for female patients.

Tests on survival curves by infection status after adjusting for gender using the three tests displayed on [Table 5](#) indicate that the survival curves were all significantly different at 5% level.

Tests on the survival curves with respect to gender adjusted for infection status; initially both male and female patients

Figure 3. Survival curves comparison by gender.

Table 4. Tests on survival curves.

Overall comparisons			
	Chi-Square	Df	Sig.
Log Rank (Mantel-Cox)	6.364	1	0.0116
Breslow (Generalized Wilcoxon)	13.954	1	0.0002
Tarone-Ware	13.326	1	0.0003
Peto-peto	11.47	1	0.0007
Fleming-Harrington*	11.23	1	0.0008

Table 5. Gender adjusted survival curves tests.

	Chi-Square	Df	Sig.
Log Rank (Mantel-Cox)	6.499	1	.011
Breslow (Generalized Wilcoxon)	13.995	1	.000
Tarone-Ware	13.607	1	.000

indicate similar survival rates from the beginning of the admission period up to about the tenth day of admission. After approximately the tenth day the female subgroup seem to portray higher survival rates up to about 45th day of admission. Stratification by patients who developed nosocomial CLABSI indicates that initially both male and female experienced similar survival rates up to approximately 6 days where the survival rates for male remain higher (see [Figure 3](#)). Three pair wise tests were conducted on survival curves with respect to gender after adjusting for infection status. Results indicate that all the three tests were not significant at 5% level.

Survival probabilities

This section portrays the survival tables for all the patients studied as well as for specific subgroups. The survival table for all the patients who were admitted into the critical care units and utilized CVCs, as provided in [Table 6](#).

Survival table for the group who were infected by CLABSI is provided in [Table 7](#).

The survival table for the patient group who did not get infected by CLABSI is shown in [Table 8](#).

Assessment of the proportional hazards (PH) assumptions done using log minus log plots, observed versus expected and goodness of fit test. Assessment of the log minus log curves by infection status indicated that they were not parallel hence violating the PH assumption. Secondly, using Observed versus Expected plots; evaluated by comparing observed (KM survival estimates) versus expected (Cox adjusted) survival curve estimates plotted on the same graph with an anticipation that they would be as close to each other as possible. Results depicted a divergence between the two curves, hence violating the assumptions of PH. Lastly, using the goodness of fit test, the results depict that only the infection status doesn't violate the PH assumption. Age, gender and number of the devices used had p-values < 0.05 indicating that violation of the PH assumption ([Table 9](#)).

Dataset 1. All raw data obtained in the present study. Columns A-K correspond with information contained in the sheet titled Variable_Info

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Discussion

Based on the results, we deduce that there is a significant difference between the lengths of stay by the patients who develop nosocomial CLABSI compared to that of patients who do not develop the infection. The patients who develop nosocomial CLABSI recorded a longer duration of stay in the hospital this in agreement with other studies conducted by^{14,2,7-10} and 11.

The proportion of patients who died after developing the nosocomial CLABSI compared to the proportion of those who died having not developed the infection revealed that there is a significant difference in the two proportions at 5% level

Table 6. Survival table for patients who utilized central venous catheters during hospitalization.

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf. Int.]	
0	0	0	1.0000	.	.	.
5	975	97	0.9090	0.0088	0.8901	0.9248
10	659	91	0.8091	0.0127	0.7828	0.8325
15	472	49	0.7384	0.0151	0.7076	0.7666
20	340	31	0.6829	0.0169	0.6484	0.7148
25	265	19	0.6396	0.0186	0.6020	0.6747
30	210	13	0.6038	0.0200	0.5633	0.6417
35	161	19	0.5439	0.0223	0.4992	0.5864
40	129	7	0.5179	0.0233	0.4714	0.5624
45	108	6	0.4922	0.0244	0.4436	0.5389
50	89	6	0.4624	0.0258	0.4113	0.5120
55	67	7	0.4206	0.0279	0.3656	0.4746
60	56	3	0.4002	0.0289	0.3433	0.4563
65	45	4	0.3681	0.0308	0.3081	0.4281
70	42	0	0.3681	0.0308	0.3081	0.4281
75	33	1	0.3569	0.0318	0.2951	0.4191
80	31	1	0.3458	0.0327	0.2824	0.4099
85	27	1	0.3339	0.0337	0.2689	0.4000
90	23	0	0.3339	0.0337	0.2689	0.4000
95	21	2	0.3035	0.0368	0.2333	0.3765
100	17	1	0.2857	0.0387	0.2125	0.3630
105	16	0	0.2857	0.0387	0.2125	0.3630
110	13	1	0.2637	0.0415	0.1863	0.3473
115	11	1	0.2417	0.0435	0.1620	0.3303
120	11	0	0.2417	0.0435	0.1620	0.3303
125	11	0	0.2417	0.0435	0.1620	0.3303
130	8	1	0.2115	0.0474	0.1273	0.3101
135	8	0	0.2115	0.0474	0.1273	0.3101
140	8	0	0.2115	0.0474	0.1273	0.3101
145	6	1	0.1763	0.0509	0.0902	0.2858
150	5	1	0.1410	0.0515	0.0594	0.2569
155	3	0	0.1410	0.0515	0.0594	0.2569
160	3	0	0.1410	0.0515	0.0594	0.2569
165	3	0	0.1410	0.0515	0.0594	0.2569
170	3	0	0.1410	0.0515	0.0594	0.2569
175	3	0	0.1410	0.0515	0.0594	0.2569
180	3	0	0.1410	0.0515	0.0594	0.2569
185	3	0	0.1410	0.0515	0.0594	0.2569
190	2	0	0.1410	0.0515	0.0594	0.2569
195	2	0	0.1410	0.0515	0.0594	0.2569
200	2	0	0.1410	0.0515	0.0594	0.2569

Note: survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

Table 7. Survival table for the infected group.

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf. Int.]	
0	0	0	1.0000	.	.	.
5	0	0	1.0000	.	.	.
10	46	1	0.9787	0.0210	0.8584	0.9970
15	44	0	0.9787	0.0210	0.8584	0.9970
20	42	1	0.9554	0.0309	0.8330	0.9887
25	40	1	0.9321	0.0379	0.8038	0.9776
30	37	2	0.8831	0.0493	0.7410	0.9497
35	34	1	0.8578	0.0540	0.7099	0.9337
40	29	6	0.7019	0.0726	0.5339	0.8190
45	26	1	0.6759	0.0744	0.5069	0.7978
50	25	0	0.6759	0.0744	0.5069	0.7978
55	22	2	0.6144	0.0793	0.4410	0.7484
60	19	1	0.5821	0.0815	0.4073	0.7218
65	16	1	0.5478	0.0836	0.3720	0.6934
70	15	0	0.5478	0.0836	0.3720	0.6934
75	12	1	0.5022	0.0882	0.3213	0.6584
80	11	1	0.4565	0.0912	0.2747	0.6214
85	10	0	0.4565	0.0912	0.2747	0.6214
90	9	0	0.4565	0.0912	0.2747	0.6214
95	9	0	0.4565	0.0912	0.2747	0.6214
100	8	1	0.3995	0.0960	0.2158	0.5775
105	7	0	0.3995	0.0960	0.2158	0.5775
110	6	1	0.3329	0.1005	0.1521	0.5261
115	4	1	0.2663	0.1000	0.0994	0.4684
120	4	0	0.2663	0.1000	0.0994	0.4684
125	4	0	0.2663	0.1000	0.0994	0.4684
130	3	0	0.2663	0.1000	0.0994	0.4684
135	3	0	0.2663	0.1000	0.0994	0.4684
140	3	0	0.2663	0.1000	0.0994	0.4684
145	2	1	0.1332	0.1066	0.0124	0.3962
150	1	1	.	.	.	.
155	1	0	.	.	.	.

Note: survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

($\chi^2_1=6.0647$, p-value=0.01379). Consequently, indicating that mortality as well as morbidity is significantly increased when a patient develops the nosocomial CLABSI, similar studies by 2,7–10,14 and 11 made a similar conclusion.

In the index study, the survival curves between those who developed an infection and those that didn't were different. This difference was not due to gender or the discharge status (alive/dead) of the patient. To the best of our knowledge no such findings have been documented in similar studies.

Table 8. Survival table for patients with no central line associated bloodstream infections.

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf. Int.]	
0	0	0	1.0000	.	.	.
5	928	97	0.9048	0.0092	0.8851	0.9213
10	614	90	0.8004	0.0132	0.7730	0.8249
15	429	49	0.7245	0.0158	0.6921	0.7541
20	299	30	0.6658	0.0178	0.6295	0.6994
25	226	18	0.6193	0.0197	0.5795	0.6566
30	175	11	0.5843	0.0212	0.5415	0.6246
35	128	18	0.5172	0.0240	0.4692	0.5631
40	102	1	0.5128	0.0242	0.4644	0.5591
45	82	5	0.4855	0.0258	0.4340	0.5350
50	65	6	0.4463	0.0283	0.3903	0.5007
55	47	5	0.4063	0.0310	0.3454	0.4663
60	37	2	0.3878	0.0322	0.3248	0.4504
65	29	3	0.3524	0.0352	0.2841	0.4212
70	27	0	0.3524	0.0352	0.2841	0.4212
75	22	0	0.3524	0.0352	0.2841	0.4212
80	21	0	0.3524	0.0352	0.2841	0.4212
85	19	1	0.3338	0.0379	0.2609	0.4083
90	15	0	0.3338	0.0379	0.2609	0.4083
95	13	2	0.2862	0.0451	0.2016	0.3762
100	12	0	0.2862	0.0451	0.2016	0.3762
105	12	0	0.2862	0.0451	0.2016	0.3762
110	8	0	0.2862	0.0451	0.2016	0.3762
115	8	0	0.2862	0.0451	0.2016	0.3762
120	8	0	0.2862	0.0451	0.2016	0.3762
125	8	0	0.2862	0.0451	0.2016	0.3762
130	6	1	0.2385	0.0575	0.1362	0.3567
135	6	0	0.2385	0.0575	0.1362	0.3567
140	6	0	0.2385	0.0575	0.1362	0.3567
145	6	0	0.2385	0.0575	0.1362	0.3567
150	6	0	0.2385	0.0575	0.1362	0.3567
155	3	0	0.2385	0.0575	0.1362	0.3567
160	3	0	0.2385	0.0575	0.1362	0.3567
165	3	0	0.2385	0.0575	0.1362	0.3567
170	3	0	0.2385	0.0575	0.1362	0.3567
175	3	0	0.2385	0.0575	0.1362	0.3567
180	3	0	0.2385	0.0575	0.1362	0.3567
185	3	0	0.2385	0.0575	0.1362	0.3567
190	2	0	0.2385	0.0575	0.1362	0.3567
195	2	0	0.2385	0.0575	0.1362	0.3567
200	2	0	0.2385	0.0575	0.1362	0.3567

Note: survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

Table 9. Goodness of fitness proportional hazards assumption test results.

	Rho	χ^2	Df	Prob> χ^2
Infection status	0.10671	3.74	1	0.0530
Gender	0.11674	5.03	1	0.0250
Age	0.14845	9.09	1	0.0026
Count of devices	0.16444	6.43	1	0.0112
global test		32.81	4	0.0000

Study limitations

The data having two subgroups that were considered in the study were disproportionate; the group (with the nosocomial CLABSI) had a very small proportion of 4.3% of the total number patients in the study compared to the proportion of the group that did not have the CLABSI infection during hospitalization. These disproportionate groups may not be very useful in survival model fitting. Searching for published journals from studies carried out in developing countries regarding survival analysis in relation to the use of CVC devices were not available.

Conclusions

The results reveal that there was a significant association between the nosocomial CLABSI infection status and the discharge status as well as the patient's length of stay. In addition, there is a difference between the survival rates of the patients who developed nosocomial CLABSI compared to those who did not. Mortality was higher among patients who developed nosocomial CLABSI compared to those who did not during their hospitalization. The duration of hospitalization (length of stay) by the patients who developed CLABSI was significantly higher compared with the duration taken (length of stay) by patients who did not develop CLABSI, which has a great impact on the financial burden the patients are subjected to due to added hospital bed days as well as medication administered.

Recommendations

Since CLABSI infections have been found to elongate patient's length of stay, appropriate strategies such as implementation of and adherence to the CVC insertion and maintenance bundles would be ideal in order to reduce the infection rates. Further matched studies in relation to CVC utilization along specific age groups and in specific diagnoses is recommended. More survival analysis research is needed in developing countries in regard to CLABSI as well as in utilization of the CVCs.

Ethical consideration

Authority to conduct the study was issued by the Ethics and Research Committee (ERC) of the participating hospital. Ethical review was conducted by the Kenyatta National Hospital/ University of Nairobi ERC, who provided approval (Ref: KNH-ERC/A/381) and an affiliation letter. Participant consent was waived since it was a retrospective study. Privacy and confidentiality was maintained by ensuring the information gathered was not relayed to anyone, but used for this study only. Patients' names were not included in the data collected and only identification numbers utilized. No risks were subjected to the patients. Direct benefit was not intended for the study population; however the results are useful in terms of adding knowledge to the existing research.

Raw data were gathered electronically and the computer used in data analysis was personalized with limited access through password protection. No public computer was utilized in data aggregation or analysis.

Data availability

F1000Research: Dataset 1. All raw data obtained in the present study. Columns A-K correspond with information contained in the sheet titled Variable_Info., <https://dx.doi.org/10.5256/f1000research.16819.d22354744>

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Thank you for this interesting report about CLABSI in Kenya. Data are rare and this publication should be acknowledged.

I have many advices to improve the format and the content of the paper:

- CLABSI definition: the definition that you used should be reported. Do you systematically performed blood culture? do you perform catheter tip culture? Recent syst review report very weak relationship between CLABSI and CRBSI and CLABSI is often a mix of CRBSI and primary bacteria with really opposite pathophysiology and impact on outcome...
- see discussion on: de Grooth HJ et al. 2019¹; see also result from **Adrie C** et al.².
- When catheter tip culture is systematically performed with the definition of CRBSI as reported by IDSA, the over risk of death is not so important. In another chapter you should explain the catheter infection policy used in your hospital, the number of single rooms the nurse to patient ratio the compliance to hands hygiene etc...
- Details on the population and more clinical characteristics should be included: at least age, severity scores, rate of mechanical ventilation, cause of ICU admission. For the catheters: site of insertion duration of catheter insertion in days
- Details on CLABSI: what are the micro-organisms recovered from blood cultures?
- Details on therapy: do you systematically removed the catheter in case of positive BC? do you start antibiotic therapy?
- Methods: as far as I understand a cox model is used. (although the figure one reverred to a progressive disability model and competing risks? Could you clarify? If it is a cox model the

method section should be largely reduced. Number at risk, time perspective? Censors? pH assumptions. If a model for competing risk is used please clearly mention the different event and the way you take into account the competing event (discharge alive?). The use of a log rank test is preferable.

- Reporting of the results: should include a table with main characteristics (see point 2 and 3); include one or 2 Kaplan Meier curves.. the table 6,7,8 should be removed. A sub analysis according to the microorganism responsible for the infection should be added.
- In the discussion you should discuss your result in view of other data on prognosis of CRBSI and CLABSI.

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Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: nosocomial infections in ICU

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 23 January 2019

<https://doi.org/10.5256/f1000research.18386.r40519>

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Gerald Mahuro

United States International University Africa, Nairobi, Kenya

The flow of the paper is good with applicable content and references to other literature. The format is well done and readable. Despite the paper informing us of what we know about extended length of stay and high probability of mortality for patients with nasocomial infections, it illuminates some statistics especially in Kenya which can be used as baseline. However, there seem to be four specific objectives for which the author has repeated (ii) twice. Kindly check the numbering and amend accordingly.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 28 Jan 2019

Francis Kiroro, Aga Khan University Hospital, Nairobi, Nairobi, Kenya

Thank you for taking time to review our paper. We will make an amendment to the numbering of the objectives.

Competing Interests: No competing interests

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