Association of high mortality with extended–spectrum β-lactamase (ESBL) positive cultures in community acquired infections

Sumit Ray, Dimple Anand, Sankalp Purwar, Arijit Samanta, Kaustubh V. Upadhye, Prasoon Gupta, Debashis Dhar

PII: S0883-9441(17)30015-1
DOI: doi:10.1016/j.jcrc.2017.10.036
Reference: YJCRC 52748

To appear in:

Please cite this article as: Sumit Ray, Dimple Anand, Sankalp Purwar, Arijit Samanta, Kaustubh V. Upadhye, Prasoon Gupta, Debashis Dhar , Association of high mortality with extended–spectrum β-lactamase (ESBL) positive cultures in community acquired infections. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Yjcrc(2017), doi:10.1016/j.jcrc.2017.10.036

Title: Association of high mortality with Extended–spectrum β-lactamase (ESBL) positive cultures in community acquired infections

Running title: ESBL status and mortality

Sumit Ray [a,b], Dimple Anand[a], Sankalp Purwar[a], Arijit Samanta[a], Kaustubh V Upadhye[a] , Prasoon Gupta, Debashis Dhar[a,b]

[a] Department of Critical Care and Emergency Medicine, Sir Ganga Ram Hospital, New Delhi-110060 (India)

[b] Department of Critical Care, City Hospital, New Delhi -110060 (India)

Corresponding Author

Dr Sumit Ray

Vice- chairperson & Senior Consultant,

Sir Ganga Ram Hospital, New Delhi-110060

Email id: drsray2014@gmail.com

Ph. No. +91 9810614433

Fax no: +91 11-45088437

Conflict of interest: No conflict of interest

Abstract

Purpose: Infections due to multidrug resistant organisms have become a serious health concern worldwide. The present study was conducted to investigate the spectrum of microbial resistance pattern in the community and their effects on mortality.

Methods: A retrospective review and analysis of prospectively collected data was done of all patients admitted with diagnosis of sepsis in two tertiary care ICU's for a period of two years. Demographics, culture positivity, microbial spectrum, resistance pattern and outcome data were collected.

Results: Out of 5309 patients enrolled; 3822 had suspected clinical infection on admission with 1452 patients growing positive microbial cultures. Among these, 201 bacterial strains were isolated from patients who had community acquired infections. 73% were Gram negative bacilli, commonest being *E.coli* (63%). 63.4% *E.coli* and 60.7% *Klebsiella* isolates were ESBL producers. The mortality in ESBL positive infections was significantly higher as compared to ESBL negative infections (Odds ratio 2.756). Moreover, ESBL positive patients empirically treated with Beta Lactams + Beta Lactamase inhibitors (BL+BLI) had significantly higher mortality as compared to patients treated with carbapenems. More data from multiple centres need to be gathered to formulate appropriate antibiotic policy for critically ill patients admitted from the community.

Keywords: ESBL positive, ESBL, BL+BLI, community-acquired infections, mortality

Introduction

Infections due to multidrug resistant (MDR) gram negative organisms particularly those producing extended spectrum β lactamases (ESBLs) are of major concern worldwide [1-4]. ESBLs are plasmid-mediated organisms - resistant to various newer generation antibiotics and can be easily transferred in the community [5]. These resistant infections pose therapeutic challenges to clinicians in the treatment of these patients and may therefore be associated with high morbidity and mortality [6,7]. Multiple studies have shown rising incidence of these ESBL organisms in health care settings [2,3,8,9]. The World Health Organization and Centre for Disease Control and Prevention guidelines have also emphasized the need of exploring incidence and associated risk factors which contribute to multidrug resistance. The Extended Prevalence of Infection in intensive care units trial (EPIC II) has revealed the extent and pattern of infection in ICUs across different geographies [10]. These studies call attention for obtaining and analysing data on multidrug resistant organisms and their impact on patient outcome. Moreover, the distinction between community-acquired and hospital-acquired infections is becoming increasingly blurred. The main reasons for this are the spread of classically 'hospital' strains, particularly MRSA and *E. Coli*, into the community and vice versa, and the repeated admissions of individuals to hospitals with long standing underlying diseases. In addition, the contribution of antibiotic resistance in the community through easily available antibiotics often used without medical supervision has resulted in an increasing reservoir of potential infections [11]. Therefore, the present study was conducted with the objective to explore the incidence of ESBL positive and MDR bacteria in the community being admitted in tertiary care ICU's in India. The mortality rates were analysed by categorizing the patients into ESBL positive versus negative; ESBL positive and MDR positive versus ESBL negative and non-MDR in the community.

Material and Methods

This was a bi-centric, observational study; conducted at two mixed medical surgical intensive care units (ICU) of super speciality tertiary care centres in New Delhi (India). Patients admitted to the ICU from July 2014-July 2016 were screened and those fulfilling inclusion criteria were enrolled. The study inclusion criteria were defined as patients >16 years admitted to the ICU; with positive cultures; cultures sent on admission or within 48 hours of admission ; no documented contact with any health care facility in the last 3 months. Patients with documented history of regular dialysis or any history of indwelling catheters were excluded.

Sample collection and processing

Blood samples were assayed for microbiological cultures. Two sets of blood cultures, urine culture, endotracheal culture (in intubated patients) were sent. For blood cultures, samples were obtained in both aerobic and anaerobic BacT/Alert bottles and performed by BacT/Alert method (bioMerieux, Marcy l' Etiole, France). Urine was procured in sterile containers. For endotracheal cultures, specimens were collected in mucus trap. Positive cultures were further processed for the identification of organisms using standard laboratory methods. Blood culture was considered positive if same organism was grown from twin cultures taken from different sites. Respiratory secretions were considered positive if many polymorphonuclear cells were present along with colony count $>10^5$. Urine culture was considered positive if there were >10 pus cells/high power field, along with single organism cultured with $>10^5$ colony forming unit/ml. Polymicrobial samples were excluded. Only one sample from each patient was considered. Coagulase negative Staphylococci were included only if positive in twin cultures from different sites. Patient demographics culture positivity, microbial spectrum, resistance patterns, acute physiology and chronic health evaluation scores (APACHE II) and outcome data were collected.

Antimicrobial treatment

All the enrolled patients had received a β-lactam (BL) + β-lactamase (BLI) combination or carbapenem. Patients with respiratory infections were additionally given macrolides or quinolones. For blood stream, urinary tract or undifferentiated infections, aminoglycosides or aztreonam were given in addition.

Antimicrobial susceptibility and ESBL testing

Antimicrobial susceptibility testing and screening test for ESBLs was performed and reports were provided by microbiologists according to the Clinical and Laboratory Standards Institute (CLSI) guidelines in Vitek-2 System (Biomerieux , Hazlewood, Mo.) using disc diffusion method. Initial screening of ESBL was indicated by a diameter of inhibition zone of ceftazdime $\leq$22 mm or cefotaxime $\leq$27mm. Furthermore, phenotypic confirmation of ESBL production was performed by testing both cefotaxime and ceftazidime alone and in combination with clavulanic acid. A greater than 3 fold concentration decrease in minimum inhibitory concentration for ceftazidime or cefepime or cefotaxime tested in combination with 4µg/ml of clavulanic acid versus its MIC (minimum inhibitory concentration) when tested alone was confirmatory for ESBL production[12].

Statistical Analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the chi square test or Fisher's exact test. To identify potential factors associated with mortality univariate analyses was performed. Multivariate logistic regression model is used to identify independent risk factors for mortality. A stepwise approach is used to enter terms into the model, with a limit of $p<0.05$ to enter the terms. The Wald test ("Wald" column) is used to determine statistical significance for each of the independent variables. Alpha level for all analyses was set as p value less than 0.05.

Results

Of the 5309 patients screened from the database admitted to ICU, 3822 (71.9%) were infected on the day of admission or within 48 hours of admission. Of the suspected infected patients, 37.9% (1452/3822) had positive microbial isolates; 13.8% (201/1452) of these culture positive patients were direct admissions from community with no documented contact with any health care facility in last 3 months and enrolled into the study.

Distribution of microorganisms

The distribution of pathogens in culture positive patients is listed in Table 1. The maximum number of isolates were from blood stream (35.3 % (71/201), followed by respiratory 31.3% (63/201) and urine (25.3%, 51/201) (Fig. 1).

Patient groups characteristics and outcome

26.8% (54/201) of infections were associated with gram-positive isolates and 73.2% (147/201) with gram-negative isolates (Fig. 2a). The most common gram-negative organisms were *Escherichia coli* (63.3%, 93/147) and *Klebsiella pneumoniae* (19%, 28/147) and the most common gram-positive organism was *Staphylo occus aureus* (51.8%, 28/54) (Table 1). Among 147 gram negative isolates, 121 were *E.coli* (n=93) and *K.pneumoniae* (n=28). Out of *taphylococcus aureus* isolates 42.8% *(*12/28) were methicillin resistant (*MRSA)*.

63.4% *E.coli* (59/93) and 60.7% (17/28) *K. pneumoniae* were ESBL positive and rest 45 (37.1%) were ESBL negative (Fig. 2b). Among remaining 26 gram negatives isolates, 7 (27%) were multidrug resistant (MDR) and 19 (73%) were non-MDR (Fig. 2c).

The characteristics of 121 patients with ESBL isolates are summarized in Table 2 (a) and combined (ESBL and MDR) isolates are shown in Table 2(b). No significant difference was observed in age, gender distribution and severity scores (APACHE II) of these patient groups (Table 2). The outcome of patients with ESBL negative and positive (n=121) and combined ESBL and MDR (n=147) is shown in Figure 3 a & b respectively. Mortality rate were significantly higher in ESBL positive (31/76) and combined positive (34/83) groups as compared to ESBL negative (9/45) and combined negative group (15/64) [Fig.3(a) & 3(b)].

The mean APACHE II score of both ESBL positive and negative infection was 25. This predicted a mortality of 56.5%. The actual mortality was 40.8% (31/76) in ESBL positive infection, while it was only 20% (9/45) in patients with ESBL negative infections. The difference was found to be statistically significant (p=0.019). Thus the actual observed mortality was significantly higher for ESBL positive patients as compared to ESBL negative patients with an odds ratio of 2.756 (95% CI: 1.16-6.52; p value: 0.021). Similarly, the mean APACHE II score of patients with combined positive status and combined negative status was also 25 but the mortality rate were significantly higher in combined positive isolates as compared to combined negative isolates with an odds ratio of 2.26 (95% CI: 1.09-4.68; p value: 0.027). Results of logistic regression are depicted in supplementary table 1.

In subgroup analysis of 76 ESBL positive patients, 38 (50%) were empirically treated with carbapenem and rest with BL+BLI. Among those Carbapenem treated patients 10 died (26.3%) and BL+BLI treated patients 21 died (55.3%). This difference is found to be statistically significant (p=0.0102). (Fig.3c).

Discussion

The most common focus of infection in our study was blood, followed by respiratory and urinary tract. In the present study 74% of the infected patients were associated with Gram-negative isolates and 26% with Gram-positive organisms. EPIC II trials also found high (62%) incidence of gram negative organisms all over the world and particularly in Asia region (74.5%). In various studies, around the world [13- 16] and India [17-19] conducted in earlier years, *S. pneumoniae* was the most common organism causing community acquired pneumonia. In EPIC II study, the most common Gram-negative organism found was *Pseudomonas* species (20%) and *E. coli* (16%). In our study, the predominant pathogens isolated were *E.coli* (46.2%) followed by *Klebsiella pneumonia* (13.9%) and *S. aureus* (13.9%). This may reflect a change in the prevalent bacteriological flora in the community over the years. This finding emphasizes the importance of collecting data to guide empiric antibiotic therapy.

Among organisms isolated from blood cultures, *E. coli* was the most common followed by *S. aureus* and *S. pneumoniae*. Our findings are consistent with study by Douglas *et al* [20] and Jordi Valles *et al* [20] Elizabeth Reddy *et al* [21] reported Salmonella as the most common organism causing blood stream infection in Africa. Among urinary specimen, most common gram negative organism was *E. coli* and most common gram positive was *E. faecium*. *E. coli* has been reported as most common community acquired urinary pathogen world over [22]. ESBL positivity among *E. coli* was 63.4% (59/93) which is high compared to other published studies in India which have reported rates from 27-56%. [23-27].

The common risk factors for community acquired MRSA infections in multiple studies include admission from another hospital, nursing home residence, intravenous drug use, prior antimicrobial use, and underlying illnesses such as cardiovascular and pulmonary disease, diabetes, malignancy, and chronic skin diseases. In our study, we noticed that 43% (12/28) of *Staphylococcus aureus* isolates were MRSA positive. Among patients with MRSA positive infection, seven were diabetics with chronic kidney disease but not on dialysis while in the rest no such high risk factors could be identified.

The striking point noted in our results is the emergence of *E.coli* as most common bacteria in the community causing bacteraemia, respiratory and urinary tract infection and higher mortality in ESBL positive producers as compared to ESBL negative producers. A high percentage (63.44%) of these *E. coli* was ESBL producers. This

high ESBL positivity probably reflects the increased resistance pattern to β Lactamase Inhibitor in hospital acquired infections due to inadvertent early use of 3rd generation cephalosporins in the last decade, which is further trickling over into the community, because of plasmid mediated transfer of its genetic materials during conjugation.

In our study, though the severity score of two sets of patients are same (APACHE II score of 25), the mortality is significantly higher in those patients infected with ESBL producing and MDR positive organisms. A retrospective cohort study by Zilberberg D Marya *et al* has found that the high mortality due to ESBL and MDR pathogens are mainly attributed by inappropriate initial antibiotic therapy, as these pathogens per se are not inherently virulent to cause higher mortality [28]. For this choice of IAAT (Initial appropriate antibiotic therapy) is more important determinant of outcome. Carbapenems are the effective choice for ESBL producing microorganisms. Though Beta-lactam + Beta-Lactamase inhibitor (BL+BLI) combinations were thought to be effective against ESBL producing organisms, but data on their clinical efficacy are limited to recommend its use regularly. FDA has approved use of these combinations in intra-abdominal sepsis and complicated urinary tract infection, but in hospital-acquired -pneumonia (HAP) its efficacy is till now not clearly proven. Again in in-vitro study it was found that ESBL strains producing TEM and SHV type beta lactamases are generally susceptible to cefepime and piperacillin tazobactam in low inoculum but in higher inoculum susceptibility patterns varies considerably. In case of CTX-M and OXA type of ESBL producing organisms, even in low inoculum size they are resistant to cefepime. In our study too we have found that 100% ESBL producing E. coli and *Klebsiella pneumoniae* are cefepime resistant. 23 out of 59 (39%) ESBL producing E. coli and 7 out of 17(41%) ESBL producing *Klebsiella pneumoniae* are BL+BLI resistant. All the ESBL producing E. coli and klebsiella were carbapenem sensitive. We started our antibiotic treatments mainly with either BL+BLI or Carbapenems in equal number of patients, but the mortality is more than double in patients received BL+BLI combinations. So in our study we have come to a conclusion that BL+BLI combination is not appropriate empirical therapy even in community acquired infection who are ESBL producing.

Our study has certain limitations. Being tertiary care centres, only 13.8% patients were admitted directly from community while rest were either referred from other health care facilities or had exposure to a healthcare facility in the last 3 months. So, despite taking years of data, the number of patients with clearly defined community acquired infections was low. Probably there was a pre-existing bias also in the infective organisms

cultured as these were critically ill patients from the community, requiring direct admission to the ICU. As critically ill patients form a small subgroup of ill patients from the community, the data may not be extrapolated to non-critically ill patients. Prospective large studies encompassing primary and tertiary care centres are required to establish the emergence of resistance patterns across the disease continuum.

Conflict of interest: None

Funding Source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1: Distribution of microorganisms on basis of site of infection

	BLOOD	**URINE**	**RESPIRATORY SECRETIONS**	**OTHERS**	**MORE THAN ONE SITE**	**TOTAL**
GRAM POSITIVE						**54**
MRSA	4	3	5	-	-	12
MSSA	7	-	8	1 (soft tissue)	-	16
S.hominis	2	-	-	-		2
S.pyogenes	1	-	-	-		1
S.pneumoniae	7	1	3	-		11
E.faecium	1	10	-	1		12
GRAM NEGATIVE						**147**
E.cloacae	2	-	2	-		4
E.coli ESBL+	20	19	13	1	6	59
E.coli ESBL-	17	10	4	3		34
K.pneumoniae ESBL+	4	3	9	1 (Bile)		17
K.pneumoniae ESBL-	2	3	6	-	-	11
P.aeroginosa	1	2	12	-	-	15
H influenzae	1	-	-	2	-	3
Ochrobactrum anthropic	2	-	-	-	-	2
Proteus mirabilis	-	-	-	1		1
Moraxella	-	-	1	-		1
TOTAL	71	51	63	10	6	**147**

Table 2: Demographic details of patient groups

a) ESBL Positive versus ESBL Negative Groups

Characteristics	ESBL Positive (n=76)	ESBL Negative (n=45)	p value
Age (Mean ± SD)	56.8 ± 14.4	54.2 ± 17.7	ns[a] (0.701)
Gender M/F	41/35	27/18	ns[b](0.517)
Survivor/ Expired	45/31	36/9	**0.019** [b]
APACHE II (Mean ± SD)	24.8 ± 10.2	24.7 ± 8.2	ns[a] **(**0.538)

Data is presented as mean ± SD (range),) or n as appropriate. Significance testing was performed by [a] student t test χ^2test[b], **p<0.005 was considered highly significant.

Abbreviations: SD, standard deviation; M, male; F, female

b) Total Positive (ESBL positive + MDR) versus Total negative (ESBL negative + non-MDR) Groups

Characteristics	Total Positive (n=83)	Total negative (n=64)	p value
Age (Mean ± SD)	56.1 ± 17.4	54.4 ± 17.4	ns[a] (0.643)
Gender M/F	47/36	39/25	s[b](0.599)
Survivor/Expired	49/34	49/15	**0.025**[b]
APACHE II (Mean ± SD)	25.1 ± 10.05	24.9 ± 8.2	ns[a](0.610)

Data is presented as mean ± SD (range),) or n as appropriate. Significance testing was performed by [a] student t test χ^2test[b], **p<0.005 was considered highly significant.

Abbreviations: SD, standard deviation; M, male; F, female

Figure Captions

Fig 1. Site of infection in culture positive patients

Fig. 2(a) Distribution of Gram positive and Gram Negative isolates

Fig. 2 (b) ESBL Status in Gram Negative isolates

Fig. 2 (c) MDR Status in Gram Negative isolates

Fig. 3(a) Correlation between ESBL status and mortality

Fig. 3(b) Correlation between ESBL + MDR status and mortality

Fig. 3(c) Correlation between ESBL positive and mortality in carbapenedm versus BL + BLI

Fig.1

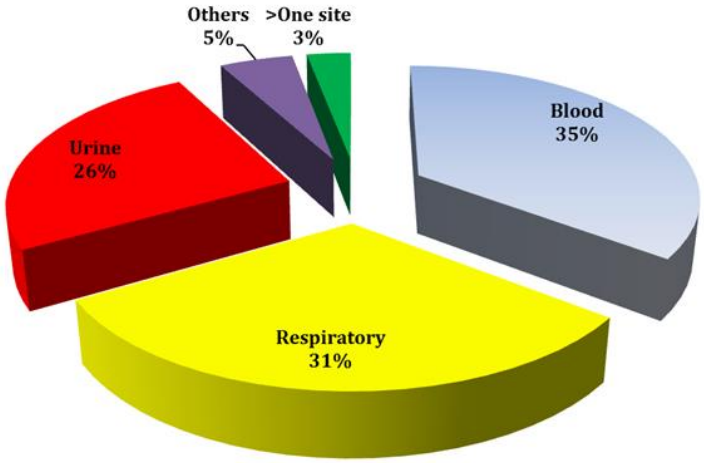


Fig. 2 (a)

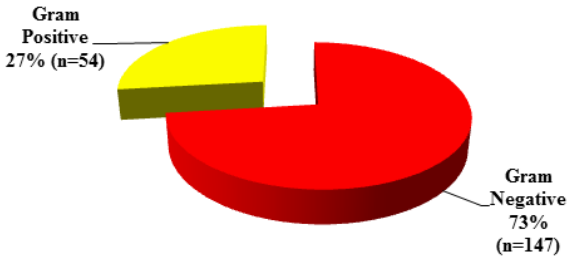


Fig. 2 (b)

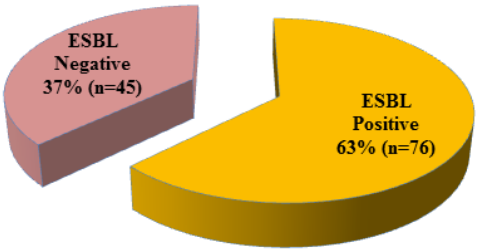


Fig. 2 (c)

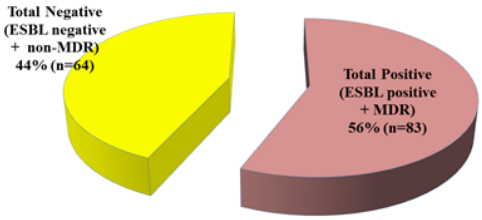


Fig. 3 (a)

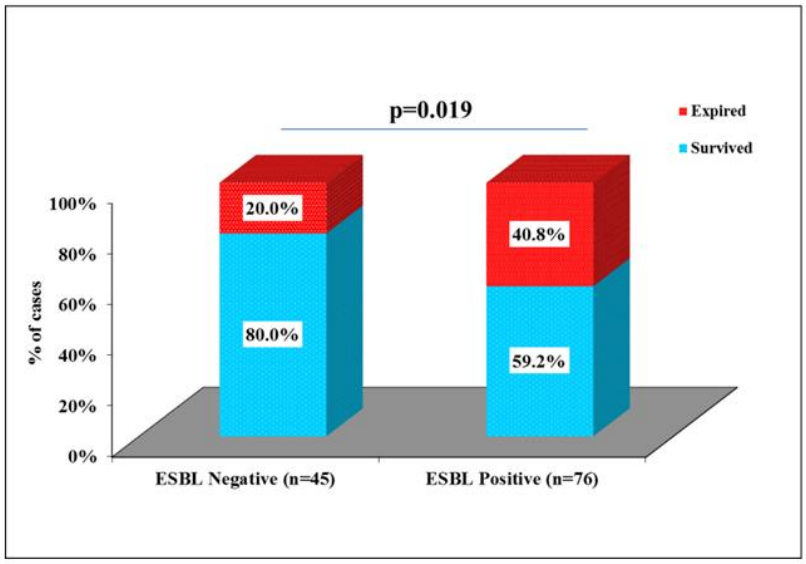


Fig. 3 (b)

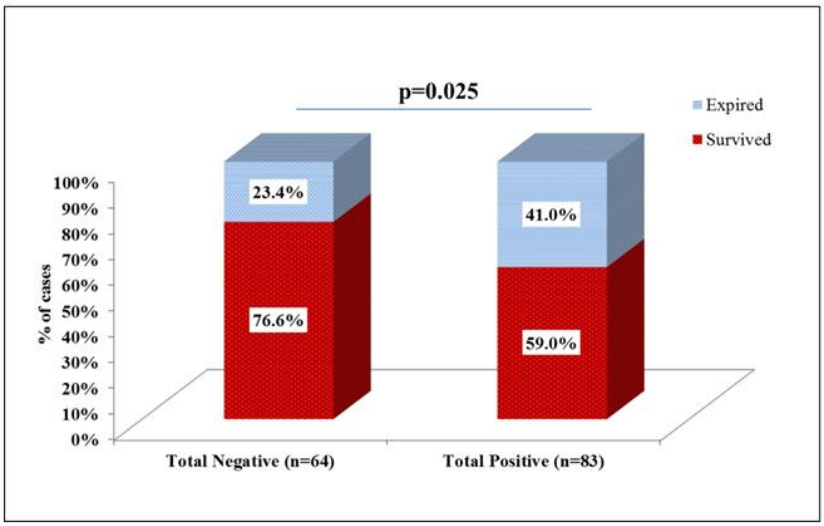
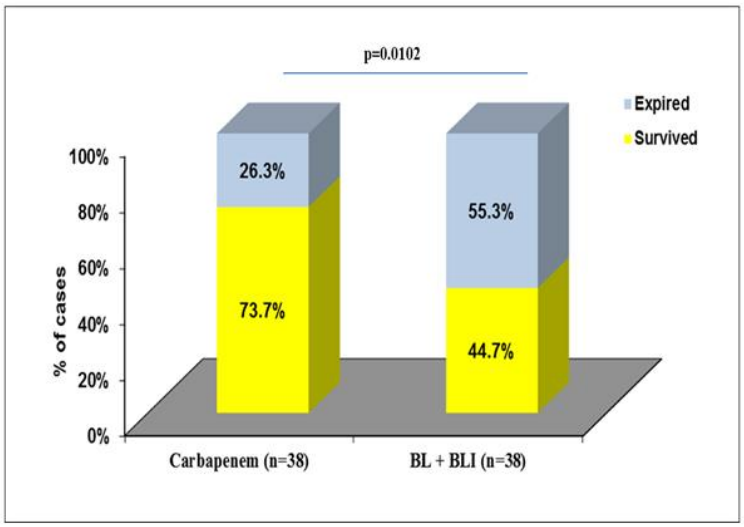


Fig. 3 (c)



Highlights

1. High incidence of ESBL producing gram negative infections from the community is worrying.

2. ESBL positive organisms found to cause higher mortality as compared to ESBL negatives.