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Section: PK/PD
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Introduction

- ❖ Extended spectrum beta-lactamase (ESBL) producing organisms pose a unique challenge for infection control contributing to increased morbidity, mortality, and healthcare costs
- ❖ Preferred agents for treatment of ESBL-producing Enterobacterales are carbapenems
- ❖ Several pharmacokinetic (PK) studies suggest hypoalbuminemia may alter the pharmacodynamics (PD) properties of ertapenem, a highly protein bound drug
- ❖ Patients with hypoalbuminemia initiated on ertapenem may experience suboptimal clinical outcomes

Objectives

- ❖ **Hypothesis:** Ertapenem usage in patients with hypoalbuminemia will lead to negative clinical outcomes such as infection recurrence, hospital readmission, and mortality when compared to subjects with higher albumin levels
- ❖ **Primary outcome:** 30-day all-cause mortality from the end of therapy with ertapenem

Methods

- ❖ Retrospective, observational, single-centered, cohort study of hospitalized patients who presented to Loyola University Medical Center between January 2010 and August 2020

Inclusion

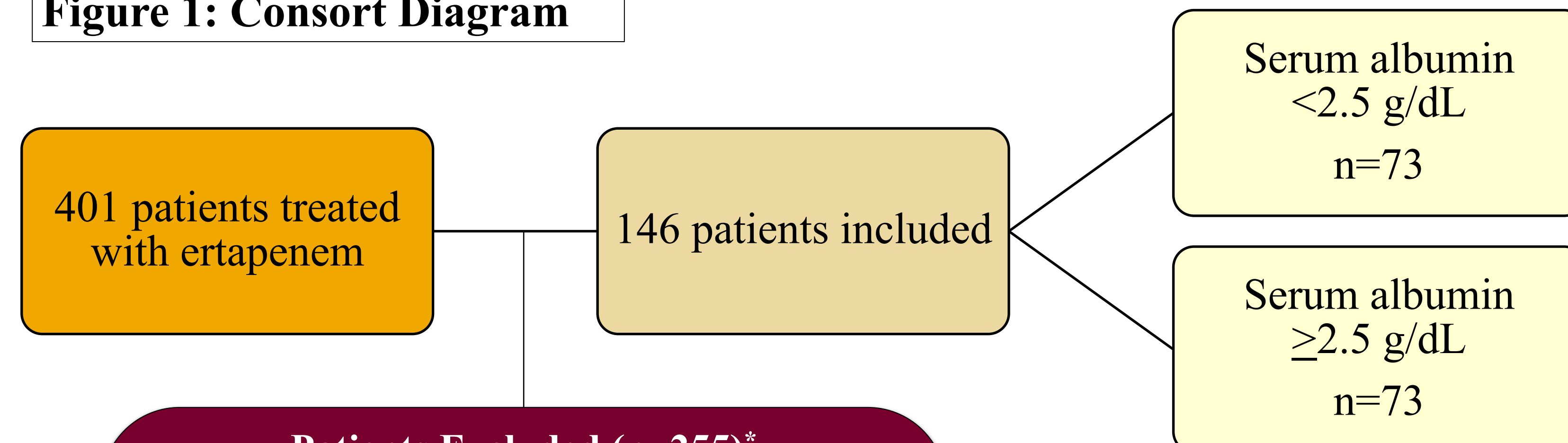
- ❖ Patients ≥18 years
- ❖ Microbiologically documented infection with susceptibility to ertapenem
- ❖ Treatment with ertapenem ≥48 hours
- ❖ Initiation of appropriate treatment within 24 hours of culture report

Exclusion

- ❖ Polymicrobial infection requiring another antibiotic where ≥1 pathogen(s) are resistant to carbapenems
- ❖ Colonization
- ❖ Ertapenem ≥72 hours after the initiation of empiric antimicrobials
- ❖ Insufficient data in EMR

Results

Figure 1: Consort Diagram



Patients Excluded (n=255)*

- Ertapenem >24h after culture results n=11
- Polymicrobial infection n=52
- Ertapenem use <48h n=16
- Ertapenem started >72h after empiric n=124
- Insufficient data in EMR n=60
- Colonization n=5
- Non-susceptible to ertapenem n=9

*Some patients met more than one exclusion criteria

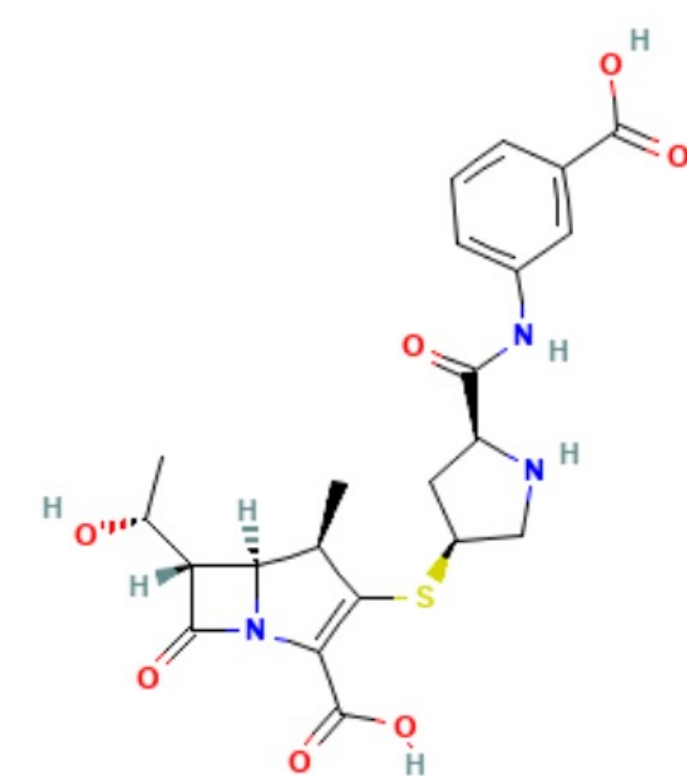


Table 1: Baseline Characteristics

| Parameter | <2.5 (g/dL) n=73 | ≥2.5 (g/dL) n=73 | P-value |
|---------------------------------------|------------------|------------------|---------|
| Age (yrs), median (IQR) | 62.3 (49.9-72.0) | 70.2 (60.5-77.1) | 0.013 |
| Sex, n (%) | | | 0.246 |
| Male | 35 (47.9) | 42 (57.5) | |
| Female | 38 (52.1) | 31 (42.5) | |
| Weight (kg), median (IQR) | 70.8 (60.2-84.4) | 74.9 (66-88.5) | 0.158 |
| Baseline SCr (mg/dL), median (IQR) | 0.95 (0.79-1.25) | 1.27 (0.9-1.7) | 0.004 |
| CrCl (mL/min), median (IQR) | 60.9 (42.4-89.9) | 41.8 (31.5-68.3) | 0.003 |
| Albumin (g/dL), median (IQR) | 2 (1.8-2.2) | 3 (2.8-3.2) | <0.001 |
| WBC (cells/L), median (IQR) | 12 (7.8-19.1) | 10.2 (6-13.3) | 0.016 |
| Temperature (°C), median (IQR) | 37.5 (37.1-38.2) | 37.5 (37-38.5) | 0.854 |
| Comorbidities, n (%) | | | |
| Congestive Heart Failure | 9 (12.3) | 11 (15.1) | 0.630 |
| Myocardial Infarction | 6 (8.2) | 4 (5.5) | 0.512 |
| Peripheral Vascular Disease | 3 (4.1) | 5 (6.8) | 0.467 |
| Stroke | 4 (5.5) | 11 (15.1) | 0.56 |
| Chronic Pulmonary Disease | 9 (12.3) | 11 (15.1) | 0.630 |
| Liver Disease | 14 (19.2) | 10 (13.7) | 0.372 |
| Cancer | 20 (27.4) | 14 (19.2) | 0.240 |
| Diabetes | 23 (31.5) | 41 (56.2) | 0.003 |
| Chronic Kidney Disease | 13 (17.8) | 28 (38.4) | 0.006 |
| HIV/AIDS | 1 (1.4) | 0 (0) | 0.316 |
| Nutrition Status, n (%) | | | |
| NPO | 10 (13.7) | 3 (4.1) | 0.42 |
| TPN | 10 (13.7) | 0 (0.0) | 0.001 |
| TF | 10 (13.7) | 5 (6.8) | 0.173 |
| General Diet | 43 (58.9) | 65 (89) | <0.001 |
| APACHE II score, median (IQR) | 13 (11-19) | 14 (10-18) | 0.613 |
| Charlson Comorbidity Index, ± mean SD | 4.60 ± 2.537 | 5.38 ± 2.782 | 0.079 |
| ICU admit, n (%) | 35 (47.9) | 18 (24.7) | 0.003 |

Table 2: Infection Related Characteristics

| Parameter | <2.5 (g/dL) n=73 | ≥2.5 (g/dL) n=73 | P-value |
|---|------------------|------------------|---------|
| Empiric therapy, n (%) | | | |
| Carbapenem | 21 (28.8) | 20 (27.4) | 0.854 |
| B-lactam | 47 (64.4) | 44 (60.3) | 0.608 |
| FQ | 4 (5.5) | 7 (9.6) | 0.347 |
| Vancomycin | 24 (32.9) | 11 (15.1) | 0.12 |
| Other | 2 (2.7) | 3 (4.1) | 0.649 |
| Empiric B-lactam, n (%) | | | |
| Cefepime | 13 (17.8) | 12 (16.4) | 0.826 |
| Zosyn | 22 (30.1) | 14 (19.2) | 0.125 |
| Aztreonam | 1 (1.4) | 0 | 0.316 |
| Ceftriaxone | 7 (9.6) | 16 (21.9) | 0.041 |
| Cefazidime | 4 (5.5) | 2 (2.7) | 0.404 |
| Empiric FQ, n (%) | | | |
| Ciprofloxacin | 4 (5.4) | 7 (9.6) | 0.347 |
| Empiric Carbapenem, n (%) | | | |
| Ertapenem | 8 (10.9) | 12 (16.4) | 0.336 |
| Meropenem | 13 (17.8) | 8 (10.9) | 0.238 |
| Isolated Pathogen, n (%) | | | |
| Gram-positive Organisms | | | |
| MSSA | 1 (1.4) | 1 (1.4) | >0.99 |
| Other gram positive | 2 (2.7) | 1 (1.4) | 0.560 |
| Gram-negative Organisms | | | |
| Citrobacter spp. | 1 (1.4) | 3 (4.1) | 0.311 |
| Enterobacter spp. | 17 (23.3) | 10 (13.7) | 0.136 |
| E.coli | 31 (42.5) | 31 (42.5) | >0.99 |
| Klebsiella spp. | 14 (19.2) | 13 (17.8) | 0.831 |
| Morganella spp. | 3 (4.1) | 3 (4.1) | >0.99 |
| Proteus spp. | 9 (12.3) | 7 (9.6) | 0.596 |
| Providencia spp. | 1 (1.4) | 1 (1.4) | >0.99 |
| Serratia spp. | 6 (8.2) | 2 (2.7) | 0.146 |
| Other gram negative | 1 (1.4) | 1 (1.4) | >0.99 |
| Anaerobic Organisms | 1 (1.4) | 2 (2.7) | 0.560 |
| Infection Source, n (%) | | | |
| Bone/joint | 3 (4.1) | 7 (9.6) | 0.190 |
| Gastrointestinal | 7 (9.6) | 6 (8.2) | 0.771 |
| Line | 7 (9.6) | 3 (4.1) | 0.190 |
| Respiratory | 7 (9.6) | 4 (5.5) | 0.347 |
| Reproductive | 0 (0) | 1 (1.4) | 0.316 |
| SSTI | 4 (5.5) | 1 (1.4) | 0.172 |
| Surgical Wound | 7 (9.6) | 0 (0) | 0.007 |
| Urinary tract | 28 (38.4) | 45 (61.6) | 0.005 |
| Unknown | 5 (6.8) | 1 (1.4) | 0.095 |
| Bacteremia, n (%) | | | |
| First negative blood culture, median (IQR) | 1.6 (1.0-2.4) | 1.5 (1.1-2.2) | 0.796 |
| Resistance Marker, n (%) | | | |
| ESBL | 41 (56.2) | 45 (61.6) | 0.501 |
| Time to initiation of ertapenem, median (IQR) | 1.9 (1.1-2.4) | 1.6 (0.2-2.2) | 0.176 |
| Time to effective therapy, median (IQR) | -0.81 (-2.6-0.1) | -1.1 (-2.5-0.01) | 0.374 |
| De-escalation, n (%) | | | |
| PO B-lactam | 8 (11.6) | 11 (16.4) | 0.417 |
| IV B-lactam | 1 (1.4) | 1 (1.4) | >0.99 |
| PO FQ | 3 (4.1) | 3 (4.1) | >0.99 |
| Other | 2 (2.7) | 5 (6.8) | 0.245 |
| Other | 2 (2.7) | 2 (2.7) | >0.99 |
| Duration of antibiotic therapy, median (IQR) | 14.9 (10.2-18.9) | 13.9 (8.2-15.9) | 0.163 |
| Duration of ertapenem therapy, median (IQR) | 12.9 (6.1-16.0) | 12.3 (5.9-14.9) | 0.447 |

Table 3: Clinical Outcomes

| Parameter | <2.5 (g/dL) n=73 | ≥2.5 (g/dL) n=73 | P-value |
|--|------------------|------------------|---------|
| Hospital length of stay, median (IQR) | 10.3 (7.2-18.2) | 6.8 (4.9-9.9) | <0.001 |
| ICU length of stay, median (IQR) | 9.2 (7.2-18.2) | 5.2 (2.1-15.9) | 0.270 |
| Infection related length of stay, median (IQR) | 8.8 (5.9-14.3) | 6.1 (4.4-8.9) | <0.001 |
| Infection recurrence, n (%) | | | |
| 30-day | 7 (9.6) | 8 (11.0) | 0.785 |
| 90-day | 14 (19.2) | 13 (17.8) | 0.831 |
| Hospital Readmission, n (%) | | | |
| 30-day | 29 (39.7) | 20 (27.4) | 0.115 |
| 90-day | 40 (54.8) | 29 (39.7) | 0.068 |
| Mortality, n (%) | | | |
| 14-day | 10 (13.7) | 5 (6.8) | 0.173 |
| 30-day | 14 (19.2) | 7 (9.6) | 0.099 |
| 90-day | 15 (20.5) | 8 (11.0) | 0.112 |

Figure 2: All-Cause Mortality

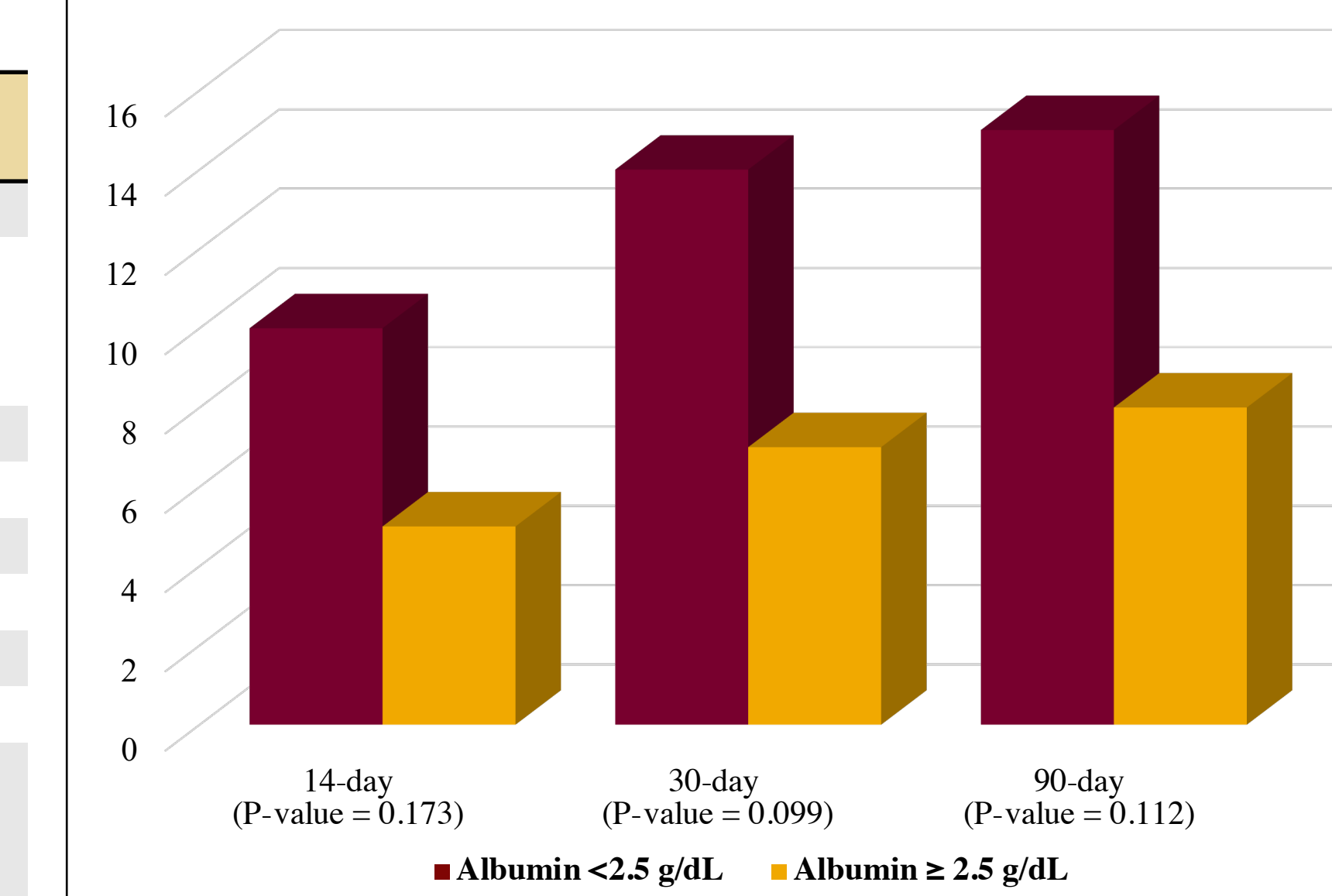


Figure 3: Length of Stay

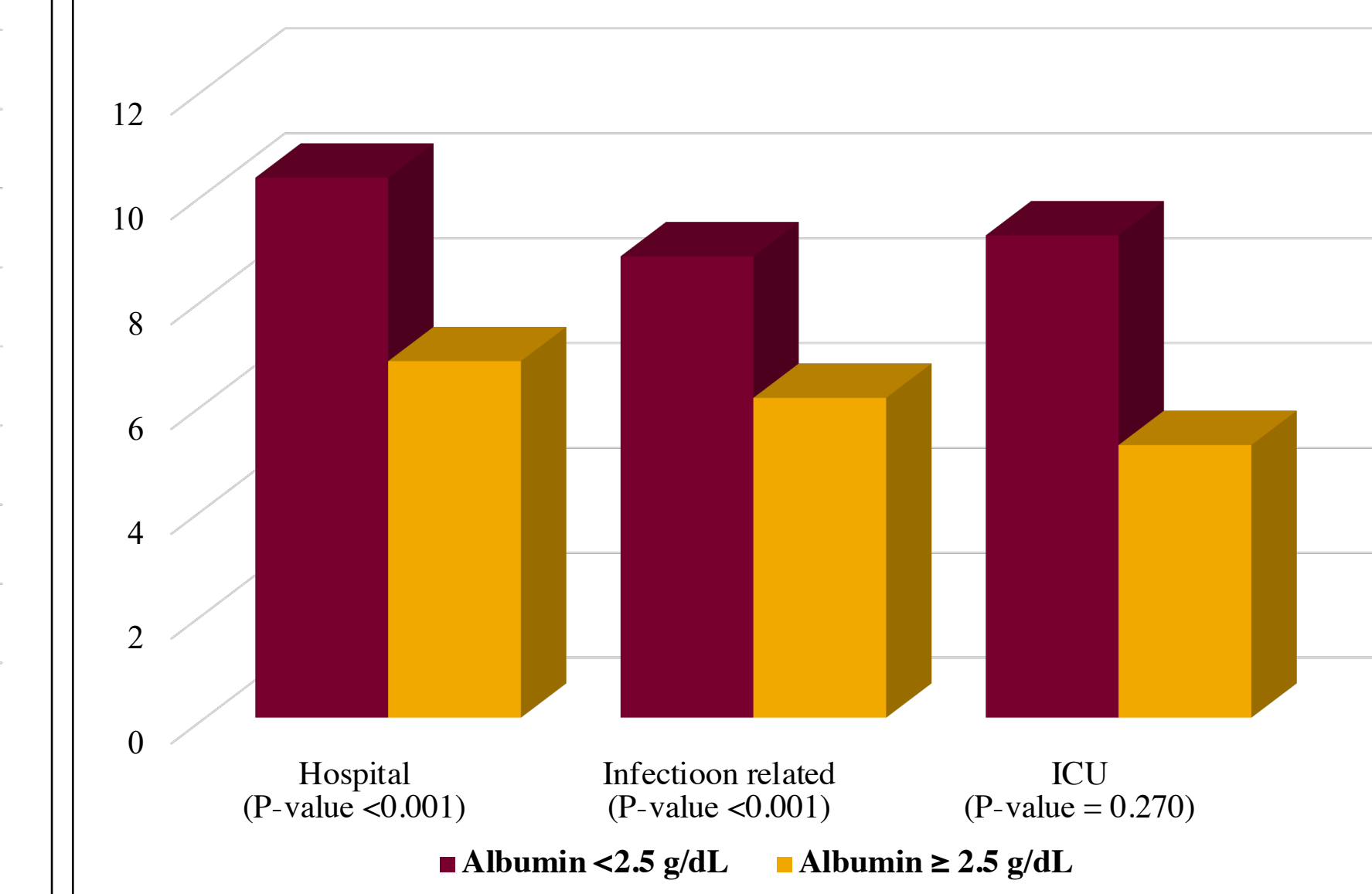
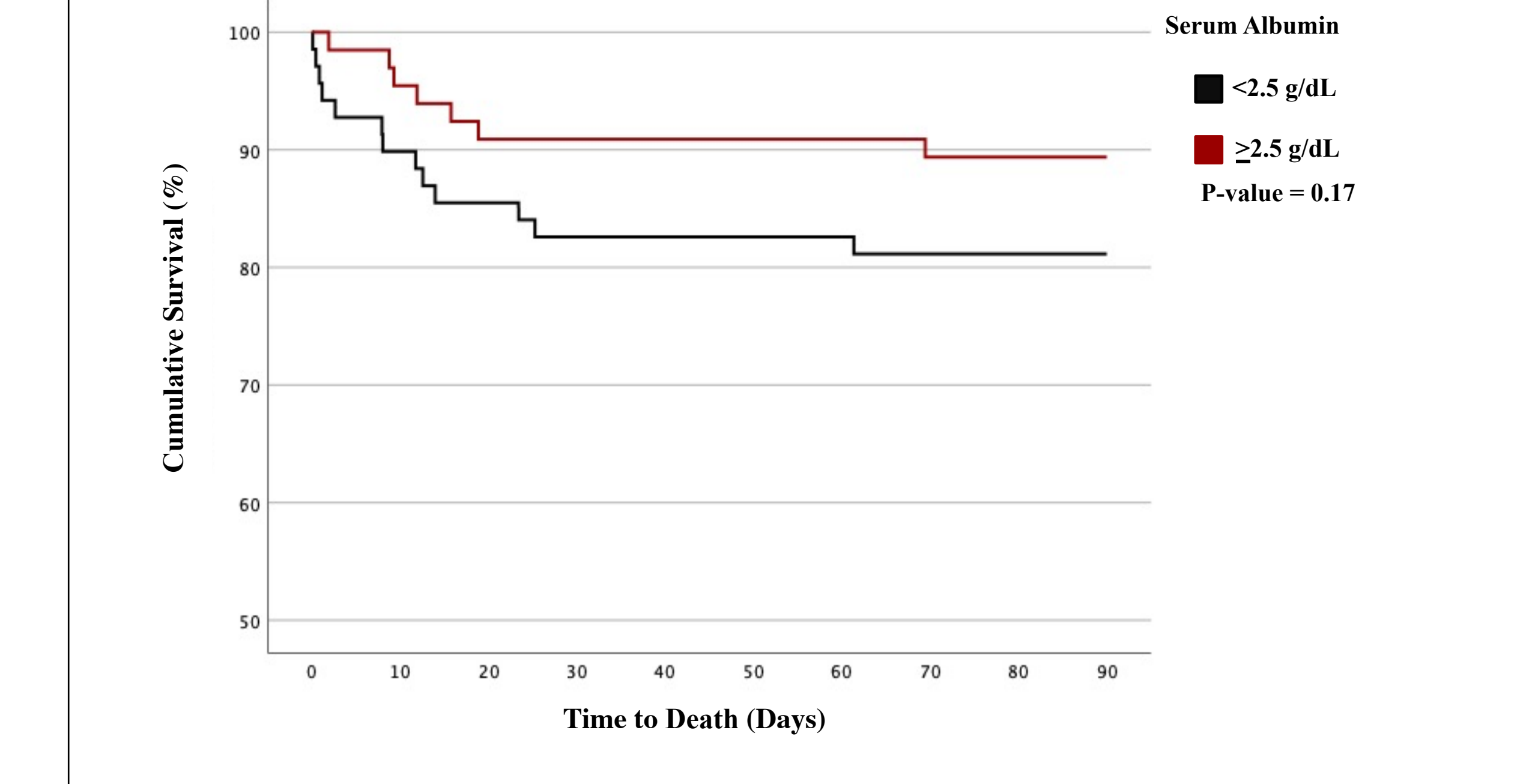


Figure 4: Kaplan-Meier Survival Curve



Limitations

- ❖ Small sample size preventing the difference in clinical outcomes between groups from reaching statistical significance
- ❖ External validity limited by single center design of study
- ❖ Ertapenem levels and PK/PD data not collected as part of present study
- ❖ Lack of control group for hypoalbuminemia patients

Conclusions and Future Directions

- ❖ No difference in APACHE II scores between groups
- ❖ Patients with normal albumin had a significantly higher Charlson Comorbidity Index
- ❖ Patients with low albumin had a significantly increased hospital LOS and infection related LOS
- ❖ Although patients with low albumin were more frequently admitted to the ICU, there was no difference in ICU LOS between groups
- ❖ In subjects with hypoalbuminemia, treatment with ertapenem dosed as a once-daily IV infusion may be associated with suboptimal clinical outcomes, trending towards higher mortality, hospital readmission, and extended length of stay
- ❖ Future studies should analyze optimal dosing strategies for ertapenem in subjects with hypoalbuminemia, as twice daily dosing may provide clinical benefit for this specific cohort