Clinical implication of vancomycin TDM in patients undergoing surgery for gastrointestinal cancer requiring mechanical ventilation: A propensity-matched analysis

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Abstract

Background: Therapeutic drug monitoring (TDM) of vancomycin is widely recommended for clinical treatment. The purpose of this study was designed to investigate the clinical implication of vancomycin TDM in patients undergoing surgery for gastrointestinal cancer requiring mechanical ventilation.

Methods: We included 78 patients who underwent surgery for gastrointestinal cancer. And all the patients included in this study were 18 years of age or older and were treated with intravenous vancomycin therapy for more than 2 days due to documented or suspected gram-positive bacterial infections, and have at least one available vancomycin plasma concentration. Based on whether the initial vancomycin concentration achieved the target trough concentration, the patients were divided into early and delayed groups and the clinical factors were compared between two groups.

Results: The research revealed that the patients undergoing surgery for gastrointestinal cancer had significantly lower initial vancomycin trough concentrations (median [IQR]: 6.90[5.28-11.20] mg/L). The duration of mechanical ventilation in early group was considerably shorter compared with delayed group ($\chi2=4.532$; $p < 0.05$; Fig 2E). Propensity score weighting further confirmed that the duration of mechanical ventilation ($\chi2=6.607$; $p < 0.05$; Fig 2F) and duration of vasoactive agent ($\chi2=6.106$; $p < 0.05$; Fig 2D) was considerably shorter compared with delayed group. Multivariate regression analysis revealed that the Cys-C was the most important variable for vancomycin target trough achievement (odds ratio, 5.274; 95% CI, 1.780 to 15.627; $p=0.003$)

Conclusions: The serum initial trough concentration of vancomycin was significantly reduced in patients undergoing surgery for gastrointestinal cancer. Minimizing the time to initial vancomycin target trough can improve clinical outcomes in Gram-positive bacterial infections. The Cystatin C (Cys-C) level is a potentially valuable parameter for predicting the vancomycin concentration and Cys-C inclusive dosing model is warranted.

Introduction

Vancomycin is a bactericidal glycopeptide antibiotic which inhibits bacterial growth by hindering the synthesis of cell wall in bacteria. It has strong antibiotic effect on Gram-positive bacteria included *methicillin-resistant Staphylococcus aureus* (MRSA), *Enterococcus*, or *methicillin-resistant Staphylococcus epidermidis* (MRSE) [6]. Intravenous vancomycin mainly combined with albumin and IgA, protein-bound protein is 25–50%, almost completely eliminated by the renal pathway. Gram-positive bacterial infections are considered one of the major causes of mortality and morbidity in patients with malignant tumors. Previous research confirmed that empirical antibacterial therapy deficiency may significantly increase infection-related morbidity and mortality of patients with malignant tumors. Still more ominously, recent evidence indicates that more than 50% of cancer patients who using vancomycin in the clinic fails to reach target concentration [7] [13]. Therapeutic drug monitoring (TDM) as an optimizing vancomycin therapy is widely recommended for avoiding secondary clinical complications because of its narrow therapeutic window, such as vancomycin toxicity due to over-dosing or resistance due to under-dosing. [The 2009 vancomycin therapeutic guideline includes recommendations for TDM to control trough concentrations (C_{trough}) of vancomycin. The recommended vancomycin dose is in the range of 15–20 mg/kg/day (actual body weight) every 8–-12 hours, with an upper limit of 2 g per dose,and the C_{trough} is 15–20 mg/L.]. Notwithstanding, the 2020 vancomycin therapeutic guideline for severe MRSA infections recommend monitoring the area under the curve (AUC) to the minimum inhibitory concentration (MIC) measured by a broth microdilution (BMD; AUC from 0 to 24 hours [AUC_{0-24}]/MIC) rather than C_{trough}[10] [5], it does not include specific recommendation about vancomycin monitoring in patients with cancer. Meanwile, Zhai et al. proposed that monitoring AUC24 is not suitable for patients with unstable renal function. Redosing when the trough concentration falls to 10-20 mg/L is a more practical method for this population. Due to the potential difficulties in availability of the Bayesian method and the feasibility of using the first-order PK equation to collect 2 steady-state samples, it is

recommended to use the same intensity trough concentration and AUC24[5].The purpose of this study was designed to investigate the clinical implication of vancomycin TDM through controlling C_{trough} in patients undergoing surgery for gastrointestinal cancer requiring mechanical ventilation.

Methods

Study design and patient population

This study was a retrospective, propensity-matched cohort study. From February 2014 to November 2018, we retrospectively reviewed 78 patients undergoing surgery for gastrointestinal cancer who were treated in the intensive care unit of Tianjin Cancer Hospital (Tianjin, China). The inclusion criteria as: aged more than 18 years, required mechanical ventilation, satisfied the sepsis-III criteria and having a Sequential Organ Failure Assessment (SOFA) score of 2 or more, were treated with intravenous vancomycin therapy for more than 3 days due to documented or suspected gram-positive bacterial infections. And exclusion criteria as: Human subjects with poor kidney function (CLcr <50 mL/min), received a single dose of vancomycin, hemodialysis patients, pregnant and lactating women. All of the enrolled patients in clinical trials received vancomycin therapy for more than five estimated terminal disposition half-lives, by which time serum vancomycin levels were supposed to have reached a steady state. Other anti-infective treatments were administered according to the patient's condition. And their data were collected from the clinical charts. This clinical trial was agreed by the Ethics Committee and approval from the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital and complied with the Declaration of Helsinki. The flow diagram is shown in Figure 1.

Vancomycin administration and therapeutic drug monitoring (TDM):

The vancomycin dosage was administered over a 1-hour period. The steady state vancomycin trough concentration was measured prior to subsequent treatment to adjust dose and dose intervals. The target serum vancomycin trough concentrations ranged from 10-15 or 15-20 mg/L [10]. Serum vancomycin concentrations were measured by fluorescence polarization immunoassay (FPIA) method using a Cobas 6000 c501 analyzer (Roche Diagnostics, China). The laboratory staff records information about each specimen, including gender, age, body weight, serum creatinine concentration, daily dosage, dose interval, infusion time, sampling time since infusion end and measure concentration for pharmacokinetic analysis.

Data collection, study definitions:

Demographic data obtained included age, gender, admission diagnosis, acute physiology and chronic health assessment II score (Apache II score) at admission to the ICU. For the treatment program, daily doses, interval time, and the occurrence of acute kidney injury (AKI) and renal replacement therapy (RRT) were recorded. New-onset acute kidney injury was defined according to the KDIGO (Kidney Disease: Improving Global Outcomes) stage II criteria after at least 24 hours and within 7 days of vancomycin administration initiation. The duration of the antibiotic and the vasoactive agent, the duration of mechanical ventilation, and the 28-day all-cause mortality were also recorded. Finally, inverse probability of treatment weighting (IPTW) was used to measure participants based on the estimated exposure probability (the propensity score) for a given confounding factor to balance the observed confounding factors between two groups[1]. The primary endpoints include the incidence of new-onset AKI or RRT, clinical success rate and 28-day all-cause mortality between two groups (early group vs. delayed group). Secondary endpoints include the duration of mechanical ventilation, the duration of antibiotics and the duration vasoactive agent.

Statistical analysis

Values for categorical variables are given as count (percentage), for continuous variables, as mean±standard deviation or as median [interquartile range]. Pearson χ^2 test was used for categorical variables, and *t* test was used for continuous variables. Univariate and multivariate analysis is used for covariates associated with target trough achievement. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. The propensity score (PS) was calculated using a multivariable logistic regression model with the two groups. Inverse probability of treatment weight (IPTW) was then calculated using PS. All statistical analyses were performed using the SPSS statistical package (version 24.0, SPSS Inc., Chicago), $p<0.05$ was considered statistically significant.

Results

A total of 1789 patients were admitted to the ICUs during the study period. And 78 patients were enrolled, all of whom received recommended standard vancomycin dosage adjustment. Clinical characteristics, drug dosage and clinical outcomes of the included patients were summarized in Table 1 and Table 2. Our research revealed that the patients undergoing surgery for gastrointestinal cancer have a significantly lower initial vancomycin trough concentration (median [IQR]: 6.90[5.28-11.20] mg/L) than the recommended standard vancomycin trough concentrations (10-15 or 15-20 mg/L) [10].

Table 1
Characteristics of patients who determined Vancomycin Therapeutic Drug Monitoring Program (n=78)

Characteristics	
Sex (male/female)	17/61
Age (years)	65[57-63]
Body weight(kg)	79[71.5-86]
Apache II score	19[18-22]
SOFA score	13[12–15]
Albumin (g/L)	28.20[24.85-32.30]
Serum creatinine (μmol/L)	56.0[46.0-84.5]
Cys-C(mg/L)	1.105[0.770-1.418]
Cancer type, n(%)	
Hepatocellular carcinoma	16(20.5)
Pancreatic cancer	6(7.7)
Colorectal cancer	22(28.2)
Gastric cancer	32(41.0)
Gallbladder cancer	2(2.6%)
Suspected source of infection	
Pulmonary	39(50)
Intra-abdominal	28(35.9)
Surgical incision	3(3.8)
Other/unknown	8(10.3)
Identified pathogens, n (%)	
methicillin-resistant Staphylococcus aureus	21(26.9)
methicillin-resistant Staphylococcus epidermidis	12(15.4)
Enterococcus	35(44.9)
Other Gram-positive *coccus*	10(12.8)

Note: Values for categorical variables are given as count (percentage); values for continuous variables as median [interquartile range].

Abbreviations:

APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment; Cys-C, Cystatin C.

Table 2
Vancomycin Dosing, Levels Achieved and Clinical Outcomes (n=78)

Characteristic	
Initial dose (daily), n (%)	
1000–2000 mg	4(5.1)
2001–3000 mg	50 (64.1)
>3000 mg	24 (30.8)
Average daily dosage (mg/kg, q12h)	15.18±3.29
	15.38[14.29-19.27]
Vancomycin trough concentration, n (%)	
<10mg/L	55 (70.5)
10-15 mg/L	15 (19.3)
15-20 mg/L	8 (10.3)
Average trough concentration (mg/L)	8.26±5.01
	6.90[5.28-11.20]
Duration of vasoactive agent(day)	4[2–5]
Duration of ventilation(day)	4[3–5]
Duration of antibiotics(day)	5[5–7]
Composite outcome of new-onset AKI or RRT	7 (9.0)
Clinical success rate, n (%)	58(74.4)
28-day all-cause mortality	4 (5.1)
Note: Values for categorical variables are given as count (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].	
Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.	

We divided patients into early group and delayed group based on whether the initial trough concentration achieved the target trough concentration. Although the Clinical outcomes were similar between two groups in Table 3 (e. g., the incidence of new-onset AKI or RRT, clinical success rate, 28-day all-cause mortality), the duration of mechanical ventilation in Early group was considerably shorter compared with Delayed group ($\chi^2 = 4.532$; $p < 0.05$; Fig. 2E). However, there was no difference between the two groups in duration of antibiotics ($\chi^2 = 1.318$; p=0.251; Fig. 2A) and of duration vasoactive agent ($\chi^2 = 2.941$; p=0.086; Fig. 2C). After IPTW method, the duration of mechanical ventilation in Early group was considerably shorter compared with Delayed group ($\chi^2 = 4.532$; $p < 0.05$; Fig. 2E). Compared with Delayed group, propensity score weighting (IPTW) further confirmed that the duration of mechanical ventilation ($\chi^2 = 6.607$; $p < 0.05$; Fig. 2F) and vasoactive agent ($\chi^2 = 6.106$; $p < 0.05$; Fig. 2D) in Early group were considerably decreased. The overall relationship between trough concentrations and potential covariates was screened by Univariate and multivariate analysis to explore potential information covariates. There was a strong correlation between vancomycin trough concentration and age, body weight, serum creatinine and serum Cystatin C level (Cys-C) (Table 4). Multivariate

regression analysis revealed that the Cys-C was the most important variable for vancomycin target trough achievement (odds ratio, 5.274; 95% CI, 1.780 to 15.627; p=0.003) (Table 4). For Delay group, all the patients made vancomycin dosage adjustment and repeated TDM daily until achieved the target therapeutic concentration.

Table 3
Patients' Baseline Data Before and After Propensity Score Weighting (n=78)

	Entire Cohort				**Propensity Score Weighting**			
Characteristics	Delayed group	Early group	χ^2	*p*	Delayed group	Early group	χ^2	*p*
	(n=55)	(n=23)			(n=23)	(n=23)		
Age,years								
Mean±S.D.	62.65±11.87	68.78±10.45		0.035*	65.22±10.76	68.78±10.45		0.260
Median(range)	65(56-70)	68(61-76)			67(60-74)	68(61-76)		
Sex,n(%)				0.542				0.381
Male	42(76.4%)	19(82.6%)			21(91.3%)	19(82.6%)		
Female	13(23.6%)	4(17.4)			2(8.7%)	4(17.4)		
Body weight,kg								
Mean±S.D.	75.53±12.38	81.61±9.302		0.038*	78.52±11.63	81.61±9.30		0.326
Median(range)	77(69-83)	84(75-88)			80(72-87)	84(75-88)		
Apache II score on ICU								
Mean±S.D.	19.51±2.73	19.65±3.60		0.849	20.00±2.73	19.65±3.60		0.714
Median(range)	19(18-22)	20(17-22)			20(17-22)	20(17-22)		
SOFA score								
Mean±S.D.	13.15±2.41	13.17±1.87		0.974	13.70±2.55	13.17±1.87		0.307
Median(range)	13[11–15]	13[12–14]			13[12–15]	13[12–14]		
Albumin (g/L)								
Mean±S.D.	27.86±5.50	28.10±6.53		0.867	27.24±3.70	28.10±6.53		0.587
Median(range)	28.0(25.7-32.3)	29.4(23.7-33.5)			27.7(25.7-29.4)	29.4(23.7-33.5)		
Serum creatinine (μmol/L)								
Mean±S.D.	62.73±29.81	79.00±26.24		0.026*	81.09±32.46	79.00±26.24		0.812
Median(range)	50(42-77)	76(63-89)			74(53-105)	76(63-89)		
Clinical Outcomes								

*$p<0.05$

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment, AKI, acute kidney injury; RRT, renal replacement therapy.

	Entire Cohort				Propensity Score Weighting			
Composite outcome of new-onset AKI or RRT	4(7.3)	3(13.0)	0.143	0.705	4(17.4)	3(13.0)	0.000	1.000
Clinical success rate, n (%)	39(70.9)	19(82.6)	1.164	0.281	16(69.6)	19(82.6)	1.075	0.300
28-day all-cause mortality	4	0	0.585	0.444	3(13.0)	1(4.3)	0.274	0.601
*p<0.05								
Abbreviations: APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment, AKI, acute kidney injury; RRT, renal replacement therapy.								

Table 4
Univariate and Multivariate Analysis of Covariates Associated With Target Trough Achievement

	Univariate Analysis			Multivariate Analysis		
Variants	OR	95% CI	*p*	OR	95% CI	*p*
Sex	1.470	0.423-5.105	0.544			
Age (years)	1.057	1.003-1.114	0.039*	1.152	0.997-1.331	0.054
Body weight(kg)	1.057	1.002-1.116	0.043*	0.929	0.804-1.073	0.315
Apache II score	1.016	0.863-1.198	0.846			
SOFA score	1.006	0.809-1.250	0.959			
Albumin (g/L)	1.007	0.925-1.097	0.864			
Serum creatinine (μmol/L)	1.018	1.002-1.035	0.032*	1.018	0.993-1.045	0.158
Cys-C(mg/L)	5.249	1.972-13.972	0.001*	5.274	1.780-15.627	0.003*
*p<0.05						
Abbreviations: APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment; Cys-C, Cystatin C.						

Discussion

Of these 78 patients undergoing surgery for gastrointestinal cancer, small number of them achieved the target trough concentration. Several explanations have been offered to explain these findings. One reason include that physiological processes are altered in patients with cancer and may alter VCM PKs [4] [3] [11] [16]. This hypothesis is supported by the existing knowledge indicating that hyperdynamic circulation caused by systemic inflammation is linked to elevated renal perfusion. Such as infection and major surgical procedures, can potentially cause systemic inflammatory response syndrome [3]. Curth et al. showed that patients with cancer could require an ~50% higher dose than the normal. This explanation is backed by studies that direct activation of renal organic anion/cation transporters (OCT1/2, OATs) by

cytokines such as TNF-α leads to an increase in renal clearance, which is confirmed by *in vivo* experiments[2] [12]. Recently, some studies have proposed augmented renal clearance (ARC) to describe the enhancement of renal elimination of circulating solutes observed in critically ill patients[14]. Most studies have shown that hyperdynamic circulation characterized by increased renal blood flow and increased in glomerular filtration rate are potential mechanism [3]. Our research also reveals that the time to achieve the target concentration of vancomycin is associated with clinical outcomes. Earlier initial goal vancomycin trough concentration achievement means shorter duration of mechanical ventilation, and shorter duration of vasoactive agent, which means earlier hemodynamic stability. Previous research confirmed that higher loading dose of vancomycin is necessary to achieve ideal therapeutic level of vancomycin. Unfortunately, this approach has the consequence of higher rates of AKI, which increases mortality. And the only modifiable risk factor for AKI was vancomycin trough level of >30 mg/L. Fortunately, TDM affords clinicians the opportunity to assess whether the dose they are providing is achieving the expected serum concentration, which may minimize the risk of nephrotoxicity and to ensure successful therapeutic outcomes. In this research, we also observed a strong correlation between vancomycin trough concentrations and the Cys-C which is a non-glycosylated, low molecular weight basic protein composed of 120 amino acids [9] [8]. Human Cys-C is a housekeeping gene and is stably produced by all human nucleated cells[9]. And recent studies confirmed that Cys-C can be very effective in predicting renal function in cancer patients [15]. And this parameter may allow physicians or pharmacists to predict vancomycin dose requirements in a short period of time. Earlier identification of insufficient vancomycin trough concentrations could be used to optimize antimicrobial adequacy. Researchers have confirmed that vancomycin dosing algorithm based on estimated glomerular filtration rate from creatinine and Cys-C levels significantly improved goal trough achievement compared to Cockcroft-Gault creatinine clearance among ICU patients with stable kidney function.

Despite these advantages, there are several potential limitations in research. Firstly, the retrospective design of the study prevents the investigation of different clinical and microbiological outcomes, nephrotoxicity, and cost. Secondly, this study was at a single center, which has the advantage of eliminating potentially confounding site specific factors, but a potential disadvantage for generalization of the results to other facilities. Thirdly, inappropriately timed vancomycin trough concentration determination is a general challenge for therapeutic drug monitoring and is present regardless of the vancomycin administration algorithm used.

Conclusion

The serum initial trough concentration of vancomycin was significantly reduced in patients undergoing surgery for gastrointestinal cancer. Clinicians should pay special attention to changes in vancomycin pharmacokinetic, and higher dosage regimens are needed to ensure clinical effectiveness. Minimizing the time to initial vancomycin target trough can improve clinical outcomes in gram positive infections. The Cys-C level is a potentially valuable parameter for predicting the vancomycin concentration and Cys-C inclusive dosing model is warranted.

Declarations

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data interpretation or writing of the manuscript.

Conflicts of interest/Competing interests

All authors reported no competing interests.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors' contributions

Xiaowu Zhang Donghao Wang were involved in the concept, interpretation of the data and writing of the manuscript. Xiaowu Zhang, Yulin Wu were involved in the statistical analyses and the writing of the manuscript.

Ethics approval

This retrospective cohort study was agreed by the Ethics Committee and approval from the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital and waived the requirement to obtain informed consent.

Consent to participate

Informed consent was obtained from all participants.

Consent for publication

All participants consented to the research and subsequent publications.

References

1. Austin PC, Stuart EA (2015) Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies Statistics in medicine. 34:3661–3679
2. Balkwill F (2009) Tumour necrosis factor and cancer. Nat Rev Cancer 9:361–371
3. Buelga DS (2005) del Mar Fernandez de Gatta M, Herrera EV, Dominguez-Gil A, Garcia MJ Population pharmacokinetic analysis of vancomycin in patients with hematological malignancies Antimicrobial agents and chemotherapy 49: 4934-4941
4. Chang D (1995) Influence of malignancy on the pharmacokinetics of vancomycin in infants and children The Pediatric infectious disease journal. 14:667–673
5. He N, Su S, Ye Z, Du G, He B, Li D, Liu Y, Yang K, Zhang X, Zhang Y, Chen X, Chen Y, Chen Z, Dong Y, Du G, Gu J, Guo D, Guo R, Hu X, Jiao Z, Li H, Liu G, Li Z, Lv Y, Lu W, Miao L, Qu J, Sun T, Tong R, Wang L, Wang M, Wang R, Wen A, Wu J, Wu X, Xu Y, Yang Y, Yang F, Zhan S, Zhang B, Zhang C, Zhang H, Zhang J, Zhang J, Zhang J, Zhang W, Zhao L, Zhao L, Zhao R, Zhao W, Zhao Z, Zhou W, Zeng XT, Zhai S (2020) Evidence-based Guideline for Therapeutic Drug Monitoring of Vancomycin: 2020 Update by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological

Society Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 71: S363-S371

6. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, M JR, Talan DA, Chambers HF (2011) Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 52:e18–55Infectious Diseases Society of A
7. Navas D, Caillon J, Batard E, Le Conte P, Kergueris MF, Moreau P, Potel G (2006) Trough serum concentrations of beta-lactam antibiotics in cancer patients: inappropriateness of conventional schedules to pharmacokinetic/pharmacodynamic properties of beta-lactams. Int J Antimicrob Agents 27:102–107
8. Ohara G, Miyazaki K, Kurishima K, Kagohashi K, Ishikawa H, Satoh H, Hizawa N (2012) Serum levels of cystatin C in elderly lung cancer patients Oncology letters. 3:303–306
9. Randers E, Erlandsen EJ (1999) Serum cystatin C as an endogenous marker of the renal function--a review Clinical chemistry and laboratory medicine. 37:389–395
10. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, Mueller BA, Pai MP, Wong-Beringer A, Rotschafer JC, Rodvold KA, Maples HD, Lomaestro BM (2020) Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists American journal of health-system pharmacy: AJHP : official journal of the American Society of Health-System Pharmacists. 77:835–864
11. Sadoh S, Tsuji Y, Tsukamoto K (2010) [Correlation of pharmacokinetic parameters with serum vancomycin concentration in elderly patients with malignancies] Yakugaku zasshi. Journal of the Pharmaceutical Society of Japan 130:69–73
12. Shimada I, Iwata C, Taga S, Teramachi H, Nomura M, Miyamoto K, Tsuciya H, Wada T, Kimura K, Matsushita R (2012) Enhanced renal clearance of vancomycin in rats with carcinogen-induced osteosarcoma Anticancer research. 32:823–829
13. Sime FB, Roberts MS, Tiong IS, Gardner JH, Lehman S, Peake SL, Hahn U, Warner MS, Roberts JA (2015) Adequacy of high-dose cefepime regimen in febrile neutropenic patients with hematological malignancies Antimicrobial agents and chemotherapy 59: 5463-5469
14. Udy AA, Roberts JA, Lipman J (2011) Implications of augmented renal clearance in critically ill patients. Nat Rev Nephrol 7:539–543
15. Yang F, Li D, Di Y, Zhang Y, Zang Y, Ren J, Yan L, Zhou Z, Liu H, Xu Z (2017) Pretreatment Serum Cystatin C Levels Predict Renal Function, but Not Tumor Characteristics, in Patients with Prostate Neoplasia BioMed research international 2017:7450459
16. Zhang X, Wang D (2020) The characteristics and impact indicator of vancomycin pharmacokinetics in cancer patients complicated with severe pneumonia. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy 26:492–497

Figures

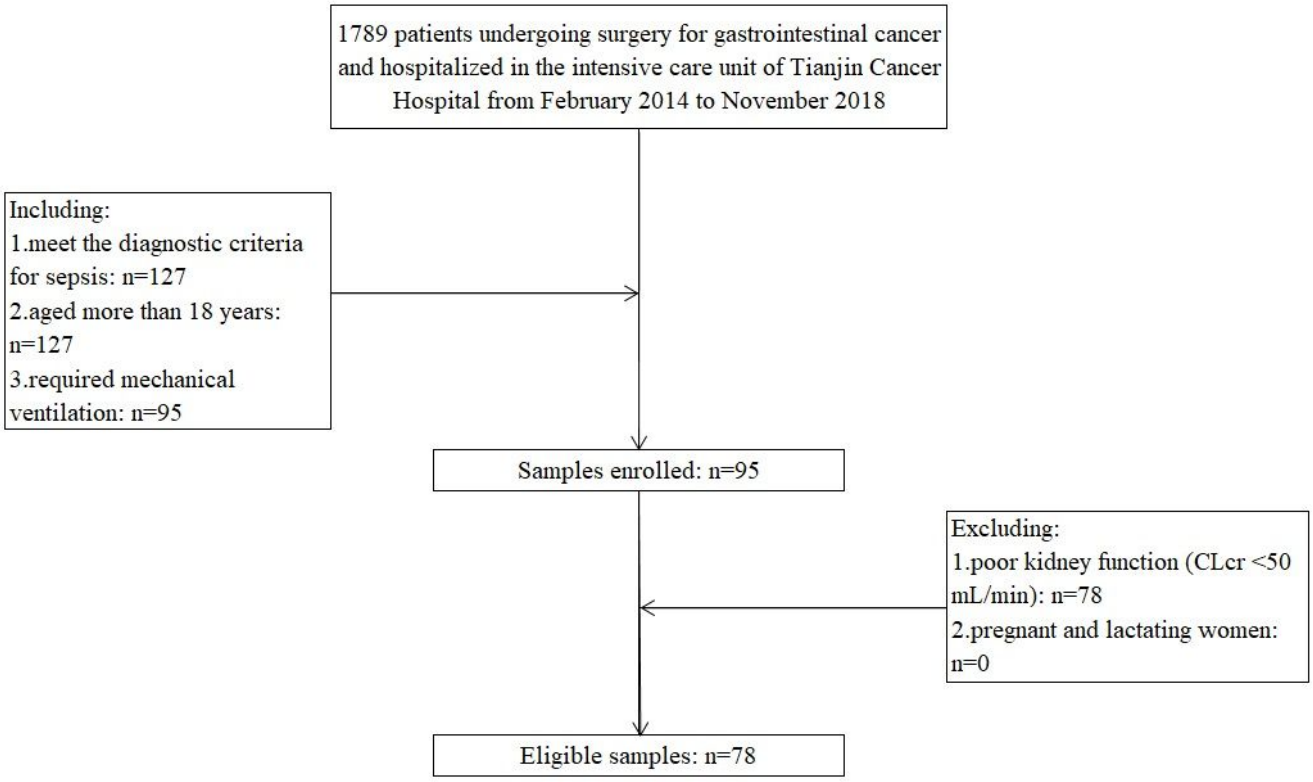

Figure 1

Enrollment of eligible samples for the study cohort.

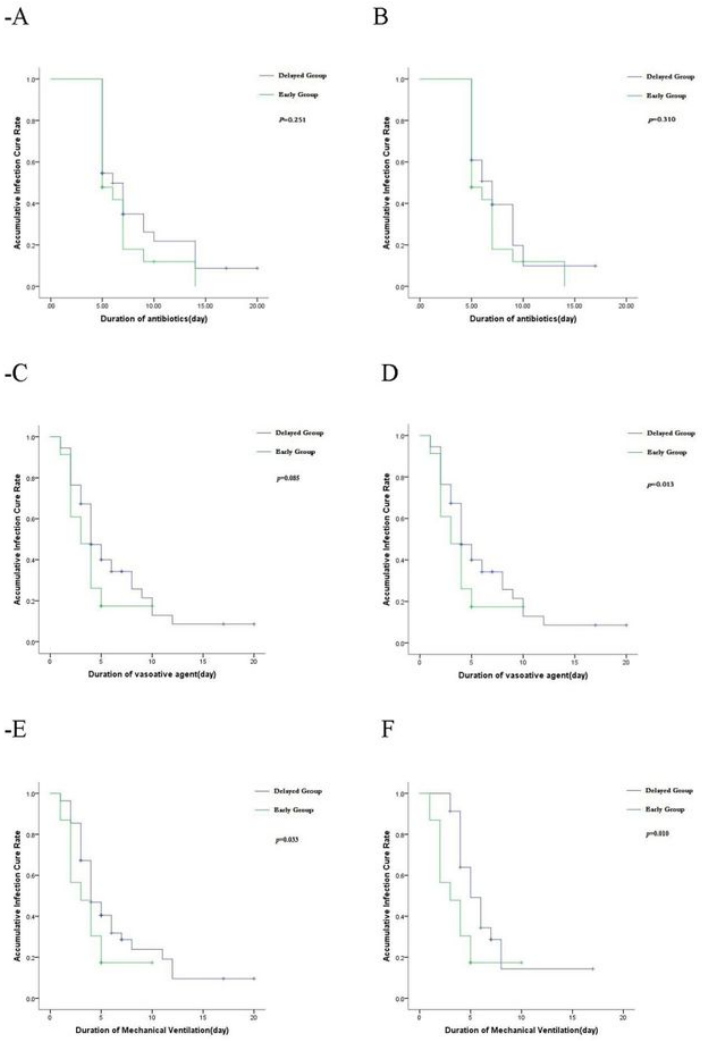

Figure 2

Kaplan-Meier curves for (A) Duration of Antibiotics between the two groups before weighting; (B) Duration of Antibiotics after weighting; (C) Duration of Vasoactive Agent between the two groups before weighting; (D) Duration of Vasoactive Agent after weighting; (E) Duration of Mechanical Ventilation between the two groups before weighting; (F) Duration of Mechanical Ventilation after weighting.