Burden and mortality of sepsis and septic shock at a high-volume, single-center in Vietnam: a retrospective study

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BACKGROUND

Sepsis and septic shock have high mortality rates and often require a prolonged hospital stay. Patient outcomes may vary according to multiple factors. We aim to determine the prevalence of antimicrobial resistance and factors associated with mortality and hospital stay.

METHODS

Clinical and microbiological data of patients with sepsis or septic shock were retrospectively collected for 15 months. Patients with negative blood cultures and patients that did not meet the SEPSIS 3 criteria were excluded.

RESULTS

We included 48 septic shock and 28 septic patients (mean APACHE II 20.32±5.61 and mean SOFA 9.41±3.17), with a mean age of 60.5 ±16.8 years and 56.6% males. WBCs, neutrophils, INR, and fibrinogen levels were significantly associated with mortality. 59.5% of the cultured bacteria were gram-negative (most common E. coli) and 27.8% were gram-positive (most common S. aureus), while 7.6% were other types of bacteria and 5.1% were fungi.

Resistance patters to gram-negative were varying, resistance to piperacillin/tazobactam, carbapenems and aminoglycosides were from 60% to 100% (A. baumanii), while they were highly sensitive to Colistin.*E. coli* was also resistant to ceftriaxone (77.8%) and sulbactam/cefoperazone (44.4%). Resistance rates for Gram-positives were high, from 86% to 100% for oxacillin, while for vancomycin, teicoplanin, and linezolid they were often low but arrived up to 42.8%. According to our logistic regression analysis, patients over 65 years-old and those who received corticosteroids had significant increased risk of in-hospital mortality (OR: 4.0; OR: 4.8).

CONCLUSION

Sepsis still poses a significant threat to patients' health, even when positive blood culture results allow the administration of specific antibiotic treatment.

Key words: sepsis, septic shock, mortality, positive blood culture.

Commented [THH1]: Line 59: study period is greater than 1 year. (April – June inclusive). This is fine but the abstract etc should reflect this accordingly.
***Reply**: Thank you for this note. We have added the relevant information about that.*
Line 6-7 "Clinical and microbiological data of patients with sepsis or septic shock were retrospectively collected during 15 months"

Commented [THH2]: Comment 2: The abstract only presents some of the resistance patterns. I suggest the authors present all the data (or a proper summary thereory) from their RESULTS section in the ABSTRACT and to be consistent in presenting all the resistance patterns where appropriate (Abstract, Results, Discussion)
Reply: we are thankful for your concern which helps improve our paper's quality, we have added an appropriate summary of these patterns in the abstract.
Line 15-19: "Resistance patters to gram-negative were varying: to piperacillin/tazobactam, carbapenems and aminoglycosides were from 60% to 100% (A. baumanii), while they were highly sensitive to colistin. E. coli was also resistant to ceftriaxone (77.8%) and sulbactam/cefoperazone (44.4%). Resistance rates for Gram-positives were high, from 86% to 100% for oxacillin, while for vancomycin, teicoplanin, and linezolid they were often low but arrived up to 42.8%"

Commented [THH3]: Comment 3: Within Abstract – I presume the last paragraph is actually "CONCLUSION"
Reply: we appreciate your comment which enhances the quality of our paper, we have added conclusion part in abstract
Line 23-24: "Conclusion: Sepsis still poses a significant threat to patients' health, even when positive blood culture results allow the administration of specific antibiotic treatment."

Introduction

Sepsis is a potentially life-threatening condition caused by an acute dysfunction of multiple organ systems due to an underlying infection. The response of the immune system causes proinflammatory mediators to accumulate at the site of infection that progressively causes a generalized reaction leading to severe systemic symptoms and disruption of normal functions (1, 2). It has been described as overwhelming intravascular inflammation that leads to an uncontrolled, unregulated, and exaggerated inflammatory response causing the inflammatory process to spread through the blood when it is normally confined to the extravascular tissue (3). Septic shock exhibits the same changes, but it represents a more severe disruption that occurs at the cellular level with metabolic parameters causing a circulatory dysfunction associated with greater mortality (1).

Sepsis can be present when a systemic inflammatory response syndrome (SIRS) is diagnosed and an infection is a probable cause, which is confirmed in culture-positive patients or suspected in culture-negative patients (4, 5). Clinically, SIRS diagnostic criteria can be applied to septic patients to predict severity, but it has been demonstrated that Sequential (Sepsis-related) Organ Failure Assessment (SOFA) scores better predict mortality risk and thus are more useful for healthcare professionals (6). The most current sepsis diagnostic criteria reflect this and have adopted the latter checklist as a reference (1, 7).

Sepsis and septic patients represent a significant burden on health systems. In terms of the effect on mortality, sepsis is responsible for 50% of hospital deaths in general (8, 9). With an estimated increase in the incidence of 8.7% per year among hospitalized patients in the United States (10), the impact on the healthcare system and overall mortality is expected to be higher in the future. As for the financial costs, the management of septic patients is expensive; although septic patients represent 3.6% of hospital stays in the United States, their expenses were more than the 13% of the total hospital costs (11). Moreover, the high risk of readmission due to recurrent sepsis among its survivors also contributes to increase its burden (12).

As previously, there were papers evaluation the characteristics of septic shock/sepsis patients with positive and negative blood culture. Besides, Phua et al. found that culture-positive sepsis was linked to more comorbidities, increased severity of illness, longer duration of hospitalization, and higher hospital and intensive care unit (ICU) mortality than culture-negative patients (4), which could be due to the early administration of effective antimicrobials or the higher rate of resistance in positive cultured patients. For those reasons, through this work we aim to describe the clinical, laboratory, and microbiological characteristics and the prevalence of antimicrobial resistance in septic and septic shock patients with positive blood cultures over a more than one-year period in the biggest hospital in Vietnam to investigate the factors related to their mortality.

Commented [THH4]: Comment 3: Line 68 why not include negative blood cultures but meeting sepsis 3 criteria? Excluding the negatives may have missed relevant cases e.g. fastidious organisms or early administration of antimicrobials. The latter may possibly bias the study, as early administration of effective antimicrobials is associated with better outcomes. You could look further at this, and potentially look for positive cultures at other sites.
***Reply**:* We are grateful for your suggestion to improve the quality of our paper. We added the explanation as below. Line 53-61 : "As previously, there were papers evaluation the characteristics of septic shock/sepsis patients with positive and negative blood culture. Besides, Phua et al. found that culture-positive sepsis was linked to more comorbidities, increased severity of illness, longer duration of hospitalization, and higher hospital and intensive care unit (ICU) mortality than culture-negative patients (4), which could be due to the early administration of effective antimicrobials or the higher rate of resistance in positive cultured patients. For those reasons, through this work we aim to describe the clinical, laboratory, and microbiological characteristics and the prevalence of antimicrobial resistance in septic and septic shock patients with positive blood cultures over a more than one-year period in the biggest hospital in Vietnam to investigate the factors related to their mortality."

Methods

Study design and settings

Data was retrospectively collected from April 01, 2019, until June 01, 2019, at the ICU department in one of the largest tertiary hospitals in Vietnam. Our protocol followed the Helsinki Declaration and international ethical standards and has been approved by the Institutional Review Board (IRB) of our Hospital and the University (ID: 19186DHYD). The collection of informed consent from the included participants was not required because of the nature of data collection.

Our hospital is the top-notch tertiary hospital in the South of Vietnam with the highest number of hospitalized patients annually in the whole country. Most of the complicated cases in the South of Vietnam would have been referred to this hospital. Due to that reason, a large percentage of referred patients received antibiotics before admission, leading to the high prevalence of antibiotic-resistant cases, especially in the critical care department.

Participants

Patients were included in the study if they: (1) received medical care over the 12 months from the start of January until the end of December 2018; (2) were 16 years or older at the time of admission at the ICU department; (3) were diagnosed by clinicians with sepsis or septic shock according to Sepsis 3 standards (1); and (4) had a positive bacterial blood culture or fungal infection. Patients were excluded if their medical records were inaccessible or deficient in the required data.

Variables, data collection, and patient outcomes

We extracted from the medical records of the included patients the following data: (1) age and gender; (2) sepsis progression (sepsis source, onset time, symptoms severity, and physical examination findings at diagnosis); (3) laboratory findings at the moment of diagnosis, including APACHE II scores; (4) microbiological findings; (5) supportive treatment and antimicrobial therapy received and (6) patient outcomes in form of survival or ICU death. To reduce the risk of including deaths for other causes, we only consider deaths in the critical care department due to sepsis/septic shock or organ failures. Deaths in patients discharged from the critical care department or death due to other causes would not be counted.

The diagnosis of sepsis and septic shock was based on Sepsis 3 criteria: a change in the SOFA scale of more than 2 points and a suspected bacterial infection based on clinical signs or identified by microbiological tests.

Patients' main cause of death was considered sepsis, if on admission to the ICU they had positive blood cultures and met SEPSIS 3 criteria, but vasopressors were not needed to maintain perfusive blood pressure. While patients registered as dead because of septic shock were septic patients with positive blood culture that also needed vasopressors to maintain an average BP of ≥ 65mmHg and

Commented [THH5]: Comment 2: To add context to the study, it would be helpful for the reader to understand the pattern of the referrals, practices at referring institutions that may influence efficacy of antibiotics, since the stated aim of the study is to determine the prevalence of antimicrobial resistance and factors associated with mortality and hospital.

*Reply: Thank you so much for your remark. We have written more to introduce the hospital
Line 70-74 "Our hospital is the top-notch tertiary hospital in the South of Vietnam with the highest number of hospitalized patients annually in the whole country. Most of the complicated cases in the South of Vietnam would have been referred to this hospital. Due to that reason, a large percentage of referred patients received antibiotics before admission, leading to the high prevalence of antibiotic-resistant cases, especially in the critical care department:"

Commented [THH6]: Comment 2: Line 67/68 was the diagnosis of sepsis / septic shock a contemporaneous diagnosis by the clinicians, or made retrospectively by the study team?
*Reply: Thank you for this note. We have added the relevant information about that
Line 78-79 "were diagnosed by clinicians with sepsis or septic shock according to Sepsis 3 standards"

Commented [THH7]: Comment 4: Line 75 what was the cutoff for mortality / outcome? Was this 30 day mortality or overall, and if the latter did you look at the ascribed cause (which may not have been related to the original sepsis)?
***Reply:** Thank you for this question. We appreciate your point. We evaluate this mortality outcome as overall ICU mortality not 30-day mortality. We added as below*
Line 86-89: *"To reduce the risk of including deaths for other causes, we only consider deaths in the critical care department due to sepsis/septic shock or organ failures. Deaths in patients discharged from the critical care department or death due to other causes would not be counted"*

had a lactate blood level > 2mmol/l (18 mg/dl), despite adequate rehydration (30 ml/kg). Treatment of sepsis/ septic shock followed the surviving sepsis campaign bundle 2018 (13) with doses of antibiotics and vasopressors based strictly on the hospital's guidelines. Sensitive to empiric antibiotics was defined as the isolated bacteria being susceptible to at least one of the antimicrobials empirically administered as the first dose or 24 hours later. Otherwise, it was considered inappropriate/resistant to empiric antibiotics (14, 15).

Data was collected anonymously and transferred to an electronic database. Patients were followed up for their entire stay at the ICU until discharge from hospital. The primary outcome of our study was patient mortality from sepsis and septic shock. Secondary outcomes were the length of stay in the ICU, clinical and laboratory parameters, causative organism characteristics, antimicrobial therapy type and duration and their correlation to patient survival.

Statistical analysis

Descriptive statistics were computed for all study variables. Regarding comparison, *Student*'s t-test and *Mann–Whitney* U-test were performed for two variable comparisons, while ANOVA and *Kruskal–Wallis* tests with *Bonferroni*'s post hoc correction were used for multiple comparisons. To assess the independent associations of clinical characteristics, underlying diseases, and microbiological risk factors with mortality, length of stay in ICU and hospital, respectively, multivariable analysis was performed. Statistical significance was concluded at a two-tailed p-value of < 0.05. Data collection was performed and completed with Epidata Entry v3.1; calculations were done using IBM SPSS Statistics.

Results

Patients' characteristics

Of the 99 patients with positive blood cultures, 76 patients met our inclusion criteria. Among them, 56.6% were females and 43.4% were males, with a mean age of 60.5 years (±16.82). Most patients were 45 years or older (72.4%) while 1% was less than 24 years old. Besides, 95% patients included in this study fall within the Center for Disease Control and Prevention definition of hospital acquired infection, namely had been admitted in another health care facility for at least 48 hours (59% in other front-line hospitals, and 36% in other Cho Ray hospital's departments) (16). While only 5% of patients had infections that could be considered community acquired (**Table 1**). Of all patients, at presentation 63.2% had a septic shock, while 36.8% had sepsis with an overall mean APACHE II and SOFA scores of 20.32 (±5.61), and 9.41 (±3.17), respectively. We had a 55.3% overall mortality rate, 76.2% of the patients that died presented on admission to the intensive care with septic shock while 23.8% fell into sepsis diagnostic criteria.

Commented [THH8]: Comment 6: Lines 87-89 need rewritten for clarity – the sentence appears incomplete.
Reply: Thank you for your advice. We edited as follows.
Line 93-97: *"Patients*' main cause of death was considered sepsis, if on admission to the ICU they had positive blood cultures and met SEPSIS 3 criteria, but vasopressors were not needed to maintain perfusive blood pressure. While patients registered as dead because of septic shock were septic patients with positive blood culture that also needed vasopressors to maintain an average BP of ≥ 65mmHg and had a lactate blood level > 2mmol/l (18 mg/dl), despite adequate rehydration (30 ml/kg)"

Commented [THH9]: Comment 1: My biggest issue is that nowhere in the manuscript is dosing mentioned. How do we know that patients weren't underdosed? The results are not consistently presented.
*Reply: we are thankful for your concern which helps improve our paper's quality. We We did not have enough data to the dosing in each patient. However, our practice based on surviving sepsis campaign bundle and hospital's guideline. I wrote it below

Commented [THH10]: Comment 7: Line 92 – prognosis is not a robust outcome measure. Do you mean status (dead or alive)? Similarly, laboratory findings, causative organism characteristics and treatment are not outcomes but are potential predictors of outcomes. This section should be rewritten.
Reply: Thank you for your advice. We edited as follows
Line 103-107: "Data was collected anonymously and transferred to an electronic database. Patients were followed up for their entire stay at the ICU until dischar

Commented [THH11]: Comment 8: Line 99-100 I'm not clear why comparison of absolute numbers with percentages is needed
Reply: Thank you for your inquiry. This is a redundancy. We have edited it to
Line 109-112 "Descriptive statistics were computed for all study variables. Regarding comparison, Student's t-test and Mann–Whitney U-test were performed for two variable comparisons, while ANOVA and Kruskal–Wallis tests wi

Commented [THH12]: Comment 9: 109-110 this sentence needs rewritten for clarity – you describe hospital associated infection but should define it clearly as such with reference to an accepted definition.
Reply: Thank you for your inputs. We have rewritten this sentence to
Line 121-124: "Besides, 95% patients included in this study fall within the Center for Disease Control and Prevention definition of hospital acquired infection, namely had been admitted in another health care facility for at least 48 h

Commented [THH13]: Comment 10: 114 defining mortality by sepsis and septic shock isn't very helpful as it is based on their initial presentation not their final moments – the final common pathway for sepsis is usually refractory septic shock
Reply: We appreciate your insights here. We have edited it to:
Line 126-129: "Of all patients, at presentation 63.2% had a septic shock, while 36.8% had sepsis with an overall mean APACHE II and SOFA scores of 20.32 (±5.61), and 9.41

The mean time of hospital stay was 21.1 (±22.8) days for patients that were discharged and 34.2 (±30.1) days for those that died (p = 0.36), while the mean time spent in the ICU was 15 (±18) and 19 (±19.6) (p = 0.04) days for these two groups, respectively.

The primary infection that started the disseminating disease occurred most often in the gastrointestinal tract (hepatobiliary sepsis, viscus perforation, etc…) (32.9%). (**Table 1**). Most had comorbidities including diabetes (47.7%) cardiovascular (32.1%), gastrointestinal (30.2%), respiratory (13.1%) diseases, and cancer or immune disorders (9.4%).

Laboratory and microbiological characteristics

All laboratory values and arterial blood gases characteristics were recorded (**Table 2**). Among the blood test parameters, there is no significant difference between two groups.

Of the 76 included patients, 22 had more than two blood cultures. However, only in three cases subsequent cultures recorded different bacterial growth (**Table 3**). The results of blood culture analysis may have been influenced by antibiotics administration before the collection of blood samples (in 56.6% of patients) as previous study strongly recommended performing blood culture prior to administrating antimicrobials due to decreasing the chance of receiving positive culture by half(17) . Among the 79 positive cultures, 59.5% detected gram-negative bacteria, 27.8% gram-positive, 7.6% other bacteria, and 5.1% contained fungal colonies.

Empiric antibiotics were used in patients with sepsis or septic shock within one hour since the diagnosis was established. The therapy of choice was based on the primary source of infection and underlying diseases. Patients with infections from the pulmonary system, for example, received meropenem or piperacillin/tazobactam. Ciprofloxacin was added to the regimen if pseudomonas infection was suspected. Gastrointestinal infected patients were treated empirically with meropenem or piperacillin/tazobactam and vancomycin and metronidazole. 46% of included cases were infected with bacteria resistant to empiric antibiotics, although in respiratory infections an empirical antibiotic therapy significantly improved the outcome of patients (p=0.017).

Among 79 positive cultures, 59.5% were for gram-negative, 27.8% for gram-positive, 7.59% for other bacteria, and 5.06% for fungi. In regard to gram negative, *Klebsiella* spp. is the leading cause with 16.45%, following that is *Acinetobacter baumannii* with 13.39% *and E.coli* with 11.39%. While, *Staphylococcus aureus* is the most common gram positive organism with 8.86%, and *Coagulase-negative staphylococcus*, *Enterococcus* spp, are the second most common with 7.69%. In order to differentiate contamination from bloodstream infection, the decision was made based on time to positive reported by microbiology laboratory, and clinical pictures. For example, the presence of symptoms leading to sepsis or patients with possible bloodstream infection vectors,

Commented [THH14]: Common 11: 116 use scientific language. Died rather than passed away.
Reply: Thank you for correcting our mistake. We have rewritten it to
Line 130-132 "The mean time of hospital stay was 21.1 (±22.8) days for patients that were discharged and 34.2 (±30.1) days for those that died (p = 0.36), while the mean time spent in the ICU was 15 (±18) and 19 (±19.6) (p = 0.04) days for these two groups, respectively."

Commented [THH15]: Comment 12: 120 can you be clearer about infections starting in the GI tract? Do you mean intra-abdominal sepsis (hepatobiliary sepsis, viscus perforation etc) rather than gastroenteritis (which would be an unusual cause of sepsis and death in adults).
**Reply: Thank you for this notice. We have added the required information about that* Line 133-134: "The primary infection that started the disseminating disease occurred most often in the gastrointestinal tract (hepatobiliary sepsis, viscus perforation, etc…) (32.9%)"

Commented [THH16]: Comment 13: 125 can you be more specific about the parameters. Presumably high white cells / neutrophils etc were associated with death, rather than just white cells per se.
**Reply: We are grateful for your notice. We have edited this sentence to*
Line 138-139: "Among the blood test parameters, there is no significant difference between two groups"

Commented [THH17]: Comment 14: 130 can you explain how blood transfusion would affect the results of blood cultures? Through contaminated blood or do you suspect that the donated blood contains antimicrobials?
**Reply: Thank you for this note. We edited this sentence to be clearer*
Line 141-145: "The results of blood culture analysis may have been influenced by antibiotics administration before the collection of blood samples (in 56.6% of patients) as previous study strongly recommended performing blood culture prior to administrating antimicrobials due to ...

Commented [THH18]: Comment 15: 133 do you know the relationship between administering antimicrobials and taking blood cultures? Was it always after drawing the blood culture?
****Reply**: We are grateful for your suggestion to improve the quality of our paper.*
Line 143-145 "as previous study strongly recommended performing blood culture prior to administrating antimicrobials as it could decrease the chance of receiving positive culture by half (17)" ...

Commented [THH19]: Comment 16: 141-145 it would be good to describe the prevalence of the individual organisms before this paragraph, to understand how the near universal betalactam resistance for ACIN and KPNE affects the study.
****Reply**: We are grateful for your suggestion to improve the quality of our paper. We have added these sentences*
Line 155-159: "Among 79 positive cultures, 59.49% were for gram-negative, 27.8% for gram-positive, 7.59% for other bacteria, and 5.06% for fungi. In regard to gram negativ ...

such as catheters are more likely to suggest Coagulase-negative staphylococcus is the cause of bloodstream infection (18).

The prevalence of antimicrobial resistance for gram-negative bacteria was 100% to piperacillin/tazobactam and carbapenems, and 90.9% to aminoglycosides for *Acinetobacter baumannii*. However, no resistance to Colistin was recorded among patients with *Acinetobacter baumannii* or *Klebsiella* spp.. *Klebsiella* spp. Had a resistance rate of more than 60% to piperacillin/tazobactam, carbapenems, and aminoglycosides.

Out of 20 cases with gram-positive bacteria, *Enterococcus* spp. And coagulase-negative *Staphylococci*. Had 100% resistance to oxacillin compared to 85.7% for *Staphylococcus aureus.* On the other hand, gram-positive bacteria were highly sensitive to vancomycin, teicoplanin, and linezolid, however, *Enterococcus* spp. Had high resistance rates of 42.8%, 42.8%, and 28.5% for the above antibiotics, respectively. Moreover, *Escherichia coli (E. coli)* was 11.11% resistant to carbapenem, 22.2% to piperacillin/tazobactam, while 100% sensitive to colistin. (**Table 3, 4**). 89.4% of patients were administered a combination of two (72.1%) or three (27.9%) antibiotics, while 10.6% had mono-antibiotic therapy. Among 76 patients, 14 patients were treated with colistin, yet there was an insignificant difference in mortality rate (p=0.452) between those that received this antibiotic and those that did not. In terms of resistance to empiric antibiotics, there were no significant difference in mortality (p=0.09) **(Table 5).**

Our logistic regression analysis demonstrated that patients' age over 65 years-old (p = 0.022), and the use of corticosteroids as a part of treatment for sepsis (p = 0.011) were significantly associated with increased length of hospital stay (OR: 3.6, 95% CI: 1-12, p = 0.04) (**Table 5, 7**). Results of the multivariate analysis of factors associated with in-hospital mortality showed that infection, corticoid use, and age 65+ years were all statistically significant factors for the outcome of in-hospital mortality (p = 0.044, 0.011, 0.022, respectively) (**Table 6**).

Discussion

The clinical definition of sepsis according to Sepsis 3 criteria is given by an increase of 2 points in the SOFA scale subsequent to an infection (6). The mean SOFA scores of patients included in our sample were 9.41 (± 3.17) and consistent with the results of Jain A et al. that analyzed patients in the hospital/ICU setting(19). The APACHE II scores assigned to our patients correlated with a higher mortality risk and the mean score in our patient's group was 20.3 (±5.61). APACHE II scores, are based on a checklist different from SOFA, elaborated for severely ill patients admitted to the ICU (20), that uses different parameters (apart from mean arterial pressure, pO2, creatinine, and Glasgow coma scale score that are in common between the two), a score > 18 on this scale it has been described as a good predictor of mortality (21). Septic shock was diagnosed when the

Commented [THH20]: Comment 17: 146 what effort did you make to determine whether coagulase negative staphylococci were causing true infection? Usually these are regarded as contaminants and would be discarded from a study like this.
**Reply: we are very grateful for your thoughts, we have written this section and added the following*
Line 160-164: "In order to differentiate contamination from bloodstream infection, the decision was made based on time to positive reported by microbiology laboratory, and clinical pictures. For example, the presence of symptoms leading to sepsis or patients with possible bloodstream infection vectors, such as catheters are more likely to suggest Coagulase-negative staphylococcus is the cause of bloodstream infection [18]"

Commented [THH21]: Comment 1: This is essentially a retrospective descriptive study. It would be much stronger if it was a cohort study comparing outcomes in those with resistant infections versus those with susceptible infection.
**Reply: We are grateful for the reviewer's perspective. This is one of the limitations of our study as this is retrospective study. According to current data that we have, we have added the statistics of resistance to empiric antibiotics in table 5.*
Line 179-180. In terms of resistance to empiric antibiotics, there were no significant difference in mortality (p=0.09) (Table 5).
Study design and setting: (line 127-130)
Sensitive to empiric antibiotics was defined as the isolated bacteria being susceptible to at least one of the antimicrobials empirically administered as the first dose or 24 hours later. Otherwise, it was considered inappropriate/resistant to empiric antibiotics (14, 15).
Discussion: (line 344-349)
In regard to resistance to empiric antibiotics, there was no significant difference in mortality between the resistance group and the sensitive group. However, in previous study, they examined the 28-day-mortality rate, which differs from the outcome of our research: all-cause ICU mortality (14). Besides, our study with a small population could not reflect the true effect of resistance to empiric antibiotics on all-cause ICU mortality. For that reason, it is necessary to have a study with a larger population examine this association.

Commented [THH22]: Comment 18: 156 was the steroid treatment for underlying disease (long term steroids) or as part of the treatment for sepsis (in which it is more likely to be an indicator of severity, rather than a predictor of outcome).
**Reply: we are very grateful for your thoughts, we have rewritten*
Line 181-183: "Our logistic regression analysis demonstrated that patients' age over 65 years-old (p = 0.022), and the use of corticosteroids as a part of treatment for sepsis (p = 0.011) were significantly associated with increased length of hospital stay (OR: 3.6, 95% CI: 1-12, p = 0.04)"

patient met the criteria for the diagnosis of sepsis and presented with low blood pressure that required the use of vasopressors to maintain an average BP of ≥ 65mmHg and lactate blood level > 2mmol / l (18mg / dl), despite adequate rehydration (30ml / kg)

The overall ICU mortality rate in our study was 55.3% which is higher than reported in previous literature (4). This difference can be most likely related to the introduction of updated sepsis diagnostic criteria (Sepsis -3) (22-24).

The mean time for hospital stay in our study was 27 (±26.91) days. This highly variable result is longer than other previously published reports but lower than others (25, 26). Many factors could influence this, including internal hospital guidelines or practices. The mean time spent in ICU was 16.8 (±18.70) days which is longer than other reports (27-29). Hospital practices on readmission to ordinary wards and on the admission of only highly critical patients could explain this discrepancy.

Age has been reported as an independent predictor of mortality in septic patients (30). Most of our patients were older than 45 years old, and 42.1% were 65 years or older. Our logistic regression analysis showed that being over 65 years of age increased the risk of in-hospital mortality (OR: 4, 95% CI: 1.2-12.9, p = 0.022). The gastrointestinal tract (hepatobiliary sepsis, viscus perforation, etc…) (32.9%) was the leading primary source of infection among our patients, in contrast to other reports in which blood borne (e.g from a implanted device) or respiratory infections prevailed (31, 32). Additionally, none of the comorbidities had statistically significant association with in-hospital mortality.

As already established, parameters correlated with acidosis and coagulopathy, known complications of septic states, were correlated with worse outcomes (33). Laboratory tests showed that the mean arterial pH, arterial HCO_3^-, and lactate levels in the surviving and deceased patients had a statistically significant difference (p = 0.019, 0.039, and 0.011, respectively). This could be explained by the fact that higher values for these parameters indicate a state of metabolic acidosis, a condition already widely reported in previous reports on septic patients (34), which is consistent with the disease progression and associated with higher mortality. Moreover, INR and fibrinogen levels had a statistically significant association with mortality (p = 0.035 and 0.02, respectively). The alteration of these parameter is suggestive of sepsis related coagulopathy and has been already reported as a factor leading to higher mortality in previous studies (35).

As expected by previous findings, procalcitonin (PCT) and C-reactive protein (CRP) levels were elevated in our patients. Declining levels of both CRP and PCT during the course of the disease, instead, were associated with a higher probability of survival (36, 37). However, it is not always a

Commented [THH23]: Comment 19: 159 the study is looking only at patients with infection. Did you compare mortality in their study population with overall hospital mortality? This should be clearer in the methods.
Rely: Thank you so much for this notice. Currently, we did not have overall hospital mortality, and we need to get IRB approval to get that data. We have edited
Line 200-201: "The overall ICU mortality rate in our study was 55.3% which is higher than reported in previous literature (4)"

Commented [THH24]: Comment 20: 181 again please be specific about the type of GIT infection (intra-abdo sepsis vs gastroenteritis)
Reply: Thank you sir for your prospective, we have edited it to
Line 212-215: "The gastrointestinal tract (hepatobiliary sepsis, viscus perforation, etc…) (32.9%) was the leading primary source of infection among our patients, in contrast to other reports in which blood borne (e.g from a implanted device) or respiratory infections prevailed [31,32]"

Commented [THH25]: Comment 21: 183/184 need rewritten for clarity – the second half is missing (a sentence starting with while should have a second clause, separated by a comma, e.g. "while none of the patients had diabetes, many of them had heart disease")
*Reply: We are very glad for this comment. The mistakes have edited to
Line 215-216: "Additionally, none of the comorbidities had statistically significant association with in-hospital mortality."

Commented [THH26]: Comment 22: 188-189 this seems obvious: acidosis and coagulopathy are expected in severe sepsis as a result of multi-organ failure
**Reply: Thank you for this notice. We have edited to*
Line: 217-218: "As already established, parameters correlated with acidosis and coagulopathy, known complications of septic states, were correlated with worse outcomes (33)"

reliable prognostic indicator and carries little significance as a standalone value. Procalcitonin values may be influenced by underlying comorbid conditions, for instance, chronic kidney disease, Procalcitonin should not viewed solely as one piece of a clinical puzzle, and is most powerful when the physician is aware of how values are influenced by the different clinical scenarios presented (38). Despite there is no significance was found in the deceased and survivors blood levels of these proteins in our study, the procalcitonin values still have a role in clinical practice when being used as a component of decision making.

It is already known that in severe sepsis the immune system is not able to contrast the widespread infection and contributes to organ dysfunction causing not only coagulopathy but also edema, organ failure, acidosis, and even shock in severe cases (39, 40). In our sample there was an insignificant difference in immune cell counts between survivors and non-survivors. We also found that autoimmune disease was a nonsignificant risk factor for both increased hospital and ICU stays in our patients (OR: 0.3, 95% CI: 0.02-2.3, p = 0.23) and (OR: 0.1, 95% CI: 0.01-1.1, p = 0.06), respectively. On the other hand, increased risk of mortality and hospital stay greater than 30 days was significantly associated with corticosteroid therapy (OR: 4.8, 95% CI: 1.4-16, p = 0.011 and OR: 3.6, 95% CI: 1-12, p = 0.04, respectively. This indicates that corticosteroid therapy should be administered with caution to decrease the negative impact on the patients' immune state as well as other side effects that could worsen prognoses, and to obtain better outcomes as already suggested in the review by Annane et al. (38). Keeping in mind that the necessity of corticosteroids use as part of the treatment for sepsis it is also likely to be an indirect indicator of increased severity of the status. Furthermore, due to the small sample, chronic kidney disease and pseudomonas infection were not significantly correlated to increased mortality rate, therefore, it is necessary to conduct studies with a larger sample size to investigate these factors.

Gram-negative bacteria (59.5%) were dominant in this study, while other studies reported alternating higher prevalence of either gram-negative or positive bacteria (41-43). Among gram-positive bacteria, up to 85.7% of *Staphylococcus aureus* were resistant to oxacillin, but the same bacteria were highly sensitive to vancomycin, teicoplanin, and linezolid. As for *Enterococcus* spp. and coagulase-negative *Staphylococci*, the rate of resistance to oxacillin was 100%, and for *Enterococcus* spp. high rates of resistance to vancomycin (42.8%), teicoplanin (42.8%) and linezolid (28.5%) were reported. *Enterococci* and especially the coagulase-negative *Staphylococci* play an important role in hospital infections (44, 45). However, the sample size in our study is modest, and thus the results of reported cases can have a limited impact. Moreover, only 42.7% of patients with Staphylococcal infections were resistant to ciprofloxacin; however while it could be an effective for many patients, it shouldn't be the first treatment of choice, due to the increased

Commented [THH27]: Comment 23: 195 the pro-calcitonin measurement is interesting and worth discussing further. All of these patients would be expected to have raised procalcitonin in keeping with positive blood cultures – was this universally the case? Did you use procalcitonin to identify infection vs contamination in blood cultures (e.g. for coag neg staph, and perhaps for some Acinetobacter cultures?)
Rely: Thank you so much for this notice. We did not solely used procalcitonin to identify infection vs contamination. We have edited the paragraph
Line 227-236 "As expected by previous findings, procalcitonin (PCT) and C-reactive protein (CRP) levels were elevated in our patients. Declining levels of both CRP and PCT during the course of the disease, instead, were associated with a higher probability of survival (36, 37). However, the trends of these factors weren't always a reliable prognostic indicator and carry little significance as a standalone value. Procalcitonin values may be influenced by underlying comorbid conditions, for instance, chronic kidney disease, Procalcitonin should be evaluated as one piece of a clinical puzzle, and is most powerful when the physician is aware of how values are influenced by the different clinical scenarios presented (38). No statistical significance was found in blood levels of these proteins among deceased and survivors in our study, nonetheless the procalcitonin values still have a role in clinical practice when being used as a component of decision making"

Commented [THH28]: Comment 18: 156 was the steroid treatment for underlying disease (long term steroids) or as part of the treatment for sepsis (in which it is more likely to be an indicator of severity, rather than a predictor of outcome).
**Reply: we are very grateful for your thoughts, we have rewritten*
Line 181-183: "Our logistic regression analysis demonstrated that patients' age over 65 years-old (p = 0.022), and the use of corticosteroids as a part of treatment for sepsis (p = 0.011) were significantly associated with increased length of hospital stay (OR: 3.6, 95% CI: 1-12, p = 0.04)"
Line 245-248 "This indicates that corticosteroid therapy should be administered with caution to decrease the negative impact on the patients' immune state as well as other side effects that could worsen prognoses, and to obtain better outcomes as already suggested in the review by Annane et al. (38). Keeping in mind that the necessity of corticosteroids use as part of the treatment for sepsis it is also likely to be an indirect indicator of increased severity of the status."

Commented [THH29]: Comment 24: 220 the statement about coag neg staph is questionable. Do you have evidence for this?
Rely: Thank you for this input. We have added references
Line 259-260 "Enterococci and especially the coagulase-negative Staphylococci play an important role in hospital infections (44, 45)"

risk of antibiotic resistance and the associated increase of isolation MRSA compared to MSSA (46, 47).

E. coli was highly resistant to many antibiotics such as ceftriaxone (77.8%), sulbactam/cefoperazone (44.4%) and sensitive to piperacillin/tazobactam (77.8%), Amikacin, ertapenem and imipenem (90%), and meropenem (100%). *Klebsiella* spp. resistance rates reached 84.6% for ceftriaxone and piperacillin/tazobactam, while lower resistance rates were found for resistance to amikacin (58.3%) and gentamicin (61.5%). It is worth noting that for *Klebsiella* spp. the rate of carbapenem resistance was very high, suggesting that the first line of treatment may be insufficient to eradicate the infection in most cases. *Acinetobacter baumannii* was 100% resistant to ceftriaxone, piperacillin/tazobactam, carbapenem, and only 10% of cultures were vulnerable to amikacin and gentamicin which makes it difficult to be eliminated. Therefore, the current recommendation of treatment using a combination of multiple antibiotic therapy should be followed rigorously, alongside the guidelines for infection control and antisepsis.

One of the main reasons leading to the high bacterial resistance is that this study was conducted in an ICU where most of the patients were previously treated in healthcare facilities, for at least 48 hours, 59% in smaller hospitals, 36% in other Cho Ray hospital's departments to the ICU and only 5% of patients were referred from the emergency department and had not been treated in other medical institutions in the days before. In regard to resistance to empiric antibiotics, there was no significant difference in mortality between the resistance group and the sensitive group. However, in previous study, they examined the 28-day-mortality rate, which differs from the outcome of our research: all-cause ICU mortality (14). Besides, our study with a small population could not reflect the true effect of resistance to empiric antibiotics on all-cause ICU mortality. For that reason, it is necessary to have a study with a larger population examine this association.

Limitations to our study were the restricted sample size, the setting in a single center and the recruitment only from the intensive care unit. In addition, the referral methods used could have brought patients with more severe conditions to the attention of our ICU compared to other centers. These factors could have led to a homogenous sample size that doesn’t reflect the heterogeneity of patients with sepsis but is more applicable to the most severe patients. Secondary outcomes such as length of stay in the ICU, and hospital wards may have been influenced by the absence of social support and by the subjective judgement of clinicians affecting final outcomes.

Microbiological analyses are of utmost importance to monitor the most prevalent pathogens and to have an updated overview of the rising resistance rates, but they cannot warrant a change of current recommendation to contain this potentially alarming phenomenon. If the results of our study were to be confirmed, more restrictions should be applied to antibiotic administration to

prevent the development of further resistances and different antibiotic regimens should be prescribed. The analysis was based on hospital documentation, so any factors that could have rendered them less reliable (such as lacking sufficient details as well as failure to convey a patient's history or poor handwriting) could have influenced our results. Moreover, some culturing was preceded by antibiotics or blood transfusion, which may have underestimated the rate of positive cultures.

Conclusion

Despite the limitations, our study reports a detailed picture of septic patients treated in Vietnamese hospitals. We recommend further studies, involving more than one center and a more varied population of septic patients to monitor severity of cases and risk factors that could be controlled or avoided. We suggest adjusting treatment approaches taking into considerations bad prognostic factors registered in our analysis when evaluating severity of admitted patients. Moreover, further studies with bigger and more heterogenous populations are required to detect present trends of antimicrobic resistance.

Commented [THH30]: Comment 4: The final statement within the text of the full manuscript (within Conclusion) is not really a conclusion and should be brought into Discussion – it certainly doesn't follow from the Results section.
*Reply: We are grateful for your suggestion to improve the quality of our paper. We moved it to the discussion.
Line 294-299: "Microbiological analyses are of utmost importance to monitor the most prevalent pathogens and to have an updated overview of the rising resistance rates, but they cannot warrant a change of current recommendation to contain this potentially alarming phenomenon. If the results of our study were to be confirmed, more restrictions should be applied to antibiotic administration to prevent the development of further resistances and different antibiotic regimens should be prescribed"

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Table 1. Baseline characteristics of all included patients and their comorbidities.

			Outcome		Total	*p*.
			Death	Survival		
Age (year)			64.3 (±17.28)	55.73 (±15.16)	60.49 (±16.82)	0.237
Gender	Male	N	11	22	33	0.099
		%	14.7%	29.3%	44.0%	
	Female	N	22	20	42	
		%	29.3%	26.7%	56.0%	
Source of infection						
Gastrointestinal system	Yes	N	16	8	24	0.174
		%	21,1%	10,5%	31,6%	
	No	N	26	26	52	
		%	34,2%	34,2%	68,4%	
Respiratory system	Yes	N	8	8	16	0.633
		%	10, 5%	10,5%	21%	
	No	N	34	26	60	
		%	44,8%	34,2%	79%	
Urinary system	Yes	N	7	9	16	0.297
		%	9,2%	11,8%	21,1%	
	No	N	35	25	60	
		%	46,1%	32,9%	79%	
Musculoskeletal, skin and connective tissue	Yes	N	6	4	10	0.746
		%	7,9%	5,3%	13,2%	
	No	N	36	30	66	
		%	47,4%	39,5%	86,9%	
Unclear	Yes	N	5	5	10	0.719
		%	6,6%	6,6%	13,2%	
	No	N	29	37	66	
		%	38,2%	48,7%	86,9%	

Table 2. Laboratory test results positive blood cultured patients with sepsis/septic shock by clinical outcome.

		Survival (n = 34)	Exitus (n = 42)	
Parameter	**Total mean (SD)**	**Mean (SD)**	**Mean (SD)**	**P -value**
CRP	155.5 (56-228.1)	189.5 (134-299)	92.1 (22.5-225.5)	0.139
PCT	16.3 (4.1-98.3)	5.7 (2.5-41.6)	38.5 (9.2-120)	0.046
Creatinine	1.7 (1.1-2.5)	1.7 (1.2-2.4)	1.8 (1-2.7)	0.975
Creatinine 24h	1.7 (1.2-2.6)	1.5 (1.2-2.6)	2 (1.2-2.7)	0.605
BUN	33 (21-44.8)	33 (23-46.1)	34.5 (21-44.3)	0.957
BUN 24h	35 (23.8-48.3)	33 (22-45.5)	37 (24.8-49.8)	0.405
ALT	43 (19.5-123)	45 (18-161.8)	36.5 (19.8-106.5)	0.967
ALT 24h	59 (33-168)	47 (27-145)	99.5 (33.3-253.5)	0.474
AST	70 (38.5-233.5)	64 (36.5-247.3)	585 (1309)	0.565
AST 24h	81 (41-269)	71 (47-233)	117 (26.5-681.3)	0.560
Bilirubin total	0.9 (0.5-1.8)	0.7 (0.4-2)	0.9 (0.7-1.5)	0.315
Bilirubin total 24h	1.4 (0.9-3.9)	1 (0.4-4.1)	1.7 (1.1-3.6)	0.320
Na^+	136 (133-142)	139 (134-145)	136 (132.8-140.3)	0.104
Na^+ 24h	137 (133-142)	140 (134.5-143)	136 (133-140.3)	0.071
K^+	3.7 (3.1-4.3)	3.6 (3.1-4.3)	3.8 (3.1-4.4)	0.877
K^+ 24h	3.6 (3.1-4.2)	3.6 (3.1-4)	3.7 (3.1-4.7)	0.376
Cl^-	103 (98-108.8)	106 (99-112)	102 (98-105.3)	0.039
Cl^- 24h	103 (99-108)	104.8 (99-110.8)	102.5 (100-105)	0.228
Albumin	2.5 (2.3-2.9)	2.5 (2.2-3)	2.5 (2.3-2.9)	0.784
pH	7.3 (7.2-7.4)	7.4 (7.2-7.4)	7.4 (7.2-7.4)	0.810
pH 24h	7.4 (7.3-7.5)	7.3 (7.2-7.4)	7.4 (7.3-7.5)	0.151
PCO_2	32.6 (24.7-40.4)	32.8 (25.4-42.9)	32.7 (24.4-39.5)	0.786
PCO_2 24h	33.7 (28.9-41.3)	33.7 (28.3-42.7)	32.7 (28.4-38.6)	0.826
PO_2	91.2 (68.5-135)	91 (63-132)	90.5 (70.3-140.4)	0.642
PO_2 24h	99.1 (79.8-149)	91.9 (73.9-151.1)	110 (88.6-150.6)	0.346
HCO_3^-	17.5 (13.1-22.5)	19.3 (14.1-22.9)	20.4 (14.6-25.3)	0.437
HCO_3^- 24h	19.4 (14.3-23.7)	19.7 (5.39)	21.4 (13.9)	0.503
PaO_2/ FiO_2	201.3 (116.6-274.5)	217.5 (68-302)	257.4 (176-323.6)	0.185
PaO_2/FiO_2 24h	237.1 (121.9-302.5)	264 (116)	231 (144)	0.517
$AaDO_2$	200.7 (123.7-260)	214.4 (182.1-270.7)	186 (100.3-240.1)	0.096

$AaDO_2$ 24h	213.5 (138.4-425.9)	245.5 (143.4-460.2)	174 (120-391.5)	0.352
Lactate	18.9 (11.7-55.1)	18.9 (13.5-29.1)	21.6 (11.3-77)	0.859
Lactate 24h (n=64)	22.6 (12.6-47)	25.6 (18.3-46.7)	20.3 (11-54.6)	0.302
Hb	96 (85-112)	103 (85-114)	93.5 (83.8-106.3)	0.339
Hb 24h	93 (79-108.5)	94 (79-110)	93 (79-107)	0.627
HCT	30 (27.4-35.7)	30.2 (27.2-37.2)	30 (27-34.5)	0.455
HCT 24h	29.1 (26.1-33.7)	28.6 (25.2-33.9)	29.1 (26.2-33.6)	0.688
WBCs	14.4 (10.8-20.5)	14.7 (11.3-19.9)	14.2 (10-20.8)	0.864
WBCs 24h	13.3 (9-21.2)	13.1 (8.6-18.2)	15.2 (9.5-22.3)	0.222
Neutrophils	11.8 (8.9-17.7)	12.6 (9.4-17.9)	11.8 (8-17.1)	0.445
Neutrophils 24h	12.8 (8.5-21.4)	11.6 (7.7-17)	15.5 (9.6-24)	0.068
Platelet	153.5 (100.3-214)	158 (111-213)	142 (90.8-215)	0.529
Platelet 24h	131 (73.5-179.5)	132 (79.5-183)	121 (67-182)	0.375
INR	1.3 (1.2-1.6)	1.3 (1.2-1.7)	1.3 (1.2-1.6)	0.756
INR 24h	1.4 (1.2-1.9)	1.4 (1.1-1.7)	1.5 (1.3-1.9)	0.093
PT	16.1 (14.5-19.8)	16.1 (14.3-19.9)	16.6 (14.6-19.2)	0.863
PT 24h	17.6 (14.5-21.2)	15.5 (14.3-18.6)	18.2 (15.5-22.1)	0.058
aPTT	32.7 (28.6-41.8)	31.7 (27.4-41.9)	34 (29.1-41.5)	0.544
aPTT 24h	38.3 (32-49)	37.9 (31.3-48.8)	38.9 (32.3-58.2)	0.833
Fibrinogen	5.2 (3.3-6.9)	5.4 (3.4-6)	4.9 (2.9-7.1)	0.973
Fibrinogen 24h	4.8 (3.1-6.4)	5.4 (3.5-6.7)	4.1 (2.4-5.6)	0.068
Blood glucose	158 (110-239)	158 (125.5-241.5)	158 (113-228)	0.811
Blood glucose 24h	165 (128-220)	162.5 (129.5-228.3)	165 (123.3-218)	0.837

PCT: procalcitonin; CRP: C-reactive protein; B.U.N: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PCO2: partial pressure of carbon dioxide; PO2: partial pressure of oxygen; PaO2: arterial partial pressure of oxygen; FiO_2: fraction of inspired oxygen; AaDO2: alveolar-arterial oxygen difference; Hb: hemoglobin; HCT: hematocrit; WBCs: white blood cells; INR: international normalized ratio; PT: prothrombin; aPTT: activated partial thromboplastin time.

Table 3. Microorganisms identified as causative agents in positive blood cultured patients with sepsis/septic shock by clinical outcome.

Microbial organism	**N**	**%**
Gram positive bacteria	22	27.8
Staphylococcus aureus	7	8.86
Coagulase-negative staphylococcus	6	7.59
***Streptococcus* spp.**	3	3.79
***Enterococcus* spp.**	6	7.59
Gram negative bacteria	47	59.49
Escherichia coli	9	11.39
***Klebsiella* spp.**	13	16.45
Proteus	1	1.26
Acinetobacter baumannii	11	13.39
Stenotrophomonas maltophillia	2	2.53
***Burkholderia* spp.**	4	5.06
***Pseudomonas* spp.**	3	3.79
Pandoraea sputorum	3	3,79
Enterobacter cloacae	1	1.26
Other bacteria	6	7.59
Fungi	4	5.06
Candida glabrata	1	1.26
Candida tropicalis	3	3.79

Table 4. Antibiotic resistance among identified microorganisms as causative agents in patients with sepsis/septic shock.

Antibiotic	***Staphylococcus aureus (%)* (n=7)**	***Coagulase-negative staphylococcus (%)* (n=6)**	***Enterococcus* spp. *(%)* (n=6)**
Oxacillin	85.70	100.00	100.00
Ciprofloxacin	42.70	100.00	100.00
Vancomycin	0.00	0.00	0.00
Teicoplanin	0.00	0.00	0.00
Linezolid	0.00	14.20	28.50

Rifampicin	0.00	28.60	85.70
	Escherichia coli (%) (n=9)	***Klebsiella* spp.** (%) (n=13)	***Acinetobacter baumannii*** (%) (n=11)
Ceftriaxone	77.78	84.6	100.00
Piperacillin/Tazobactam	22.22	84.6	100.00
Sulbactam/Cefoperazone	44.44	76.9	72.72
Ertapenem	11.11	92.3	100.00
Imipenem	11.11	76.9	100.00
Meropenem	0.00	76.9	100.00
Gentamicin	33.33	61.5	90.9
Amikacin	22.22	53.8	909
Trimethoprim/Sulfamethoxazol	77.78	46.1	72.72
Colistin	0.00	0.00	0.00

Table 5. Clinal outcomes of positive-blood cultured positive patients with sepsis/septic shock

		Survivor (n = 34)	**Death (n = 42)**	**p (overall)**
ICU time (days)		19.0 (19.6)	15.0 (18.0)	0.360
Time in hospital (days)		34.2 (30.1)	21.1 (22.8)	0.040
Outcomes				0.017
Sepsis		18 (52.9%)	10 (23.8%)	
Shock sepsis		16 (47.1%)	32 (76.2%)	
Empiric antibiotics	Resistant	12	23	0.09
	Sensitive	22	19	

Table 6. Risk adjusted logistic regression model of in-hospital mortality

Variables	**β**	**OR**	**95% CI**	**P-value**
Infection (sepsis/septic shock)	1.138	3.1	1.0 – 9.4	**0.044**
Corticoid use	1.572	4.8	1.4 – 16	**0.011**
Chronic kidney disease	-0.840	0.4	0.06 – 3	0.4
Pseudomonas	-0.308	0.7	0.04 – 11.9	0.8

Age > 65	1.380	4	1.2 – 12.9	**0.022**

Table 7. Risk adjusted logistic regression model of ICU stay > 14 days

Variables	β	OR	95% CI	P-value
Infection (sepsis/septic shock)	-0.335	0.7	0.2 – 2.1	0.5
Corticoid use	1.041	2.8	0.9 – 8.9	0.07
Autoimmune disease	-2.094	0.1	0.01 – 1.1	0.06
Age > 65	1.210	3.3	1.1 – 9.9	**0.029**

Variables	β	OR	95% CI	P-value
Infection (sepsis/septic shock)	-0.035	0.9	0.3 - 3	0.95
Corticoid use	1.276	3.6	1 - 12	**0.04**
Autoimmune disease	-1.337	0.3	0.02 – 2.3	0.23
Age > 65	-0.077	0.9	0.3 – 2.8	0.89
Chronic kidney disease	-0.267	0.8	0.1 – 4.4	0.8

Table 8. Resistance to empirical antibiotics by source of infection

			Outcome		Total	*p.*
			Death	Survival		
Source of infection						
Gastrointestinal system	Resistant	N	10	2	12	0.083
		%	41%	8%		
	Sensitive	N	6	6	12	
		%	24%	24%	50%	
Respiratory system	Resistant	N	7	2	9	***0.017***
		%	44%	12%		
	Sensitive	N	1	6	7	
		%	6%	37%		
Urinary system	Resistant	N	2	3	5	0.838
		%	12%	19%		
	Sensitive	N	5	6	11	
		%	31%	37%		
Musculoskeletal, skin and connective tissue	Resistant	N	1	3	4	0.065
		%	10%	30%		
	Sensitive	N	5	1	6	
		%	50%	10%		
Unclear	Resistant	N	3	2	5	0.527
		%	30%	20%		
	Sensitive	N	2	3	5	
		%	20%	30%		