

# Investigating the Economic Fallout of Hospital-Acquired Infections and Multidrug-Resistant Organisms of Neonatal Sepsis at a Chinese NICU

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## Review Article

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## ABSTRACT

**Introduction:** Neonatal sepsis refers to a condition in newborns characterized by systematic inflammation caused by an infection, leading to higher rates of illness and death in neonatal intensive care units worldwide. Despite extensive research on its causes, the financial costs associated with this harmful occurrence, particularly healthcare associated and multidrug resistant sepsis in neonatal intensive care units, have not been thoroughly assessed. This study was carried out to estimate the economic consequences of newborn sepsis of newborn sepsis among neonates hospitalized to intensive care units at a general hospital in Taizhou, Zhejiang, China.

**Methods:** A hospital based case control study with retrospective medical records review was conducted among admitted newborns at the neonatal intensive care unit in Taizhou hospital. The study population consisted of 6,507 neonates who were admitted between January 1<sup>st</sup>, 2020, and December 31<sup>st</sup>, 2022. Among these neonates, we identified 155 cases of sepsis. To ensure comparability, we used the propensity score matching technique to match each septic case with four controls, resulting in a total of 620 controls. We then compared the length of hospitalization and the overall financial burden among neonates with Hospital-Acquired sepsis (HAI-sepsis), sepsis caused by Multidrug Resistant Organisms (MDRO-sepsis), and those without sepsis.

**Results:** The overall incidence of neonatal sepsis was 2.4%. Hospital-acquired sepsis (HAI-sepsis) was associated with an additional cost of \$6,287 (95% CI: 2,372-11,688), while sepsis caused by multidrug-resistant organisms (MDRO-sepsis) incurred an extra expense of \$15,199 (95% CI: 9,450-18,511). Moreover, HAI-sepsis and MDRO-sepsis were found to significantly prolong the length of hospital stay by 31 (95% CI: 16-43), and 41 days (95% CI: 31-50), respectively.

**Conclusion:** This study highlights the substantial financial implications of

nosocomial infections. It underscores the importance of implementing antimicrobial stewardship and preventive measures against healthcare associated infections in Neonatal Intensive Care Units (NICUs) to effectively reduce healthcare resources utilization and enhance the efficiency of services provided.

**Keywords:** NICU; Neonatal sepsis; Hospital acquired infection; Multidrug resistance organism; Economic impact

**Abbreviations:** CLBSI: Central-Line Bloodstream Infection; COVID-19: Corona Virus Disease 2019; GDP: Gross Domestic Product; HAI: Hospital Acquired Infection; LOS: Length of Hospital Stay; MDRO: Multidrug Resistance Organism; NICU: Neonatal Intensive Care Unit; PSM: Propensity Score Matching; SMD: Standardized Mean Difference.

## INTRODUCTION

The world health organization asserted that the abuse of antibiotics and subsequent development of multidrug-resistant organisms pose a serious threat to global public health and the advancements of contemporary medicine. The infant's established natural flora may change because of the frequent and inappropriate antibiotic prescription, and bacteria that are multi-antibiotic resistant may also arise. Newborns are extremely vulnerable to infections, and septicaemia or septic shock can be life-taking. However, the hospital acquired sepsis and MDR-sepsis can be reduced by a well-developed hospital infection control program and empowered antimicrobial stewardship at the institutional level [1].

The diagnostic and therapeutic challenges in neonatal infections have sustainably existed in NICUs. Neonatal sepsis can manifest as non-typical symptoms and signs that could also be brought on by non-infectious conditions (such as apnea, congenital heart disease, or gastroesophageal reflux syndrome). The absence of infection-related indications during the newborn's physical examination does not rule it out [2]. Additionally, there are no laboratory tests that can confidently confirm or isolate a possible early organism. Consequently, the administration of empirical antimicrobials, which is a frequent and widely acceptable technique as in NICU clinical practice. However, the pathogens of neonatal infections vary due to the etiologic pathway. And it is controversial that empirical antimicrobials are used in asymptomatic neonatal infections whose mother diagnosed with chorioamnionitis [3].

Neonatal sepsis, especially MDRO-sepsis are posing a great threat on neonatology department. The World Health Organization has reported that sepsis ranked the third of the leading cause of mortality in newborns. However, in some developing countries (such as India), neonatal sepsis contributed to the most of neonatal deaths. In China, the incidence of neonatal sepsis was estimated to be 25.6 per 1000 live births at national average levels, and sepsis or meningitis contributed to 1.4% of the neonatal mortality, ranking the 7<sup>th</sup> leading cause [4]. Various studies have revealed that MDR-sepsis escalated the mortality in NICU. It was evaluated that the detected rate of MDROs in neonatal sepsis was higher than that of national average levels [5].

The clinical consequences of neonatal sepsis have been studied intensively; however, quantitative research has rarely investigated the economic burden of sepsis in neonates [6]. The objective of this study is to quantify the monetary impacts attributable to nosocomial sepsis and MDR-sepsis at NICU in Zhejiang Taizhou hospital [7].

## LITERATURE REVIEW

### Study design

This was a retrospective case-control study using propensity score matching. This study was conducted at neonatal intensive care unit at Zhejiang Taizhou Hospital, a referral teaching hospital located in Taizhou, Zhejiang, China [8]. Data was collected through the hospital information system and the hospital acquired infection surveillance system and the department of medical statistics. The operation period of the study was from January 1<sup>st</sup>, 2020, to December 31<sup>st</sup>, 2022 [9].

### Selection criteria of the study population

All patients who were admitted to NICU during the study period (n=6,507) were included in the study. Patients who died or were released from the hospital within 24 hours of admission (n=13) and patients who were born more than 4 weeks (n=3) were not included [10]. The final sample included 6,491 eligible observations. The decision of “sepsis” diagnose was made by the qualified neonatologists under the diagnoses of “septicemia”, “septic shock”, “neonatal sepsis”. Hospital-acquired infection septic cases were identified by trained neonatologists and reported through the online healthcare associated infection surveillance system, and subsequently verified by the hospital acquired infection control and management group, using diagnostic criteria issued by the ministry of health of the people's republic of China [11]. Multidrug resistance organism septic cases were those patients who were isolated with pathogens resistant to 3 types of antimicrobials in the laboratory. Medical expenditure data were collected from the medical record statistics department [12]. A flow chart detailing the selection and exclusion process for propensity score matching was provided.

### Statistical analysis

The statistical analysis for this study was conducted using R software (version 4.0.3). A total of 6,491 neonates who met the selection criteria were included in the matching process. Propensity Score Matching (PSM) was utilized to match the neonatal sepsis cases with four control subjects [13]. The PSM method took into account the following covariates including age in days, gender, birth weight, premature, low birth weight, operation, and co-morbidities such as respiratory failure, acute respiratory distress syndromes, twin babies, hemolytic jaundice, neonatal wet lung, hyperbilirubinemia, hypoglycemia, renal pelvis anomalies, and anemia. The process was carried out using the “MacthIt” R package, employing the “nearest neighbour” method without replacement. The package can be installed within the software. Logistic regression propensity scores were computed for each participant based on the aforementioned confounding factors [14].

The 155 cases of newborn sepsis were then matched with four control subjects using propensity scores that were closest within a range of 0.1 standard deviation (with a calliper of 0.1). Subsequently, balanced diagnostic evaluations were performed and visually represented. The septic cases were further categorized as non-HAI and HAI sepsis, as well as non-MDRO and MDRO sepsis [15]. Following this, comparisons were made across groups in terms of total medical expenses, including each sub item, as well as the length of hospital stay. The estimation of median differences was accomplished using a resampling technique. By conducting 2000 bootstrap iterations, median differences between the groups were calculated along with a 95% confidence interval [16]. In cases where data was missing, the values were replaced with a zero-cost, and these missing values were not factored into the calculations. Non-parametric statistical methods (median and interquartile range) were employed to interpret the monetary findings while considering the absence of missing data [17].

To evaluate the differences between the sepsis and non-sepsis groups, statistical analysis was performed using the Mann-Whitney U test for non-normally distributed covariates such as age (measured in days) and birth weight (measured in

kilograms). The  $\chi^2$  test was employed for categorical variables. A significance level of  $p<0.05$ , with two tailed analysis, was considered statistically significant [18].

All financial data was gathered and recorded in Chinese currency (RMB) and subsequently converted to United States Dollars using the average exchange rate for the years 2020 to 2022, which equated to 1 US dollar being equivalent to 6.7 RMB [19].

## RESULTS

The study included a total of 6,491 neonates admitted for at least 24 hours during the 3 years study period showed that the overall economic burden of neonatal sepsis in the study population was 0.89 million US dollars, with an average cost of \$5,771 per episode. MDRO-sepsis and nosocomial sepsis have escalated the medical cost, which represented \$16,230 and \$11,410 per episode, respectively. The attack rate of neonatal sepsis was 24 per 1000 admissions, where the incidence of HAI-sepsis and MDR-sepsis were 3.2/1000 and 1.5/1000.

The demographic and clinical distributions of the sample were displayed. The statistics showed that the original sample was not balanced regarding more than half of the confounders. However, after propensity score matching process, the adjusted cohorts were 93% balanced based on 15 proposed covariates. The plot was generated according to absolute Standardized Mean Difference (SMD). All covariates were within  $\pm 1$  SMD demonstrating an appreciated matching output.

Of these, 155 confirmed septic cases consisted of 21 HAI-sepsis and 134 non-HAI sepsis. The median medical expenditure is \$8,720 for HAI neonatal sepsis and \$1,901 for non-septic newborns. The significance incremental cost was found in each sub item due to nosocomial sepsis. Non-HAI sepsis partially increased surgical, laboratory testing expenses, however, it was not significantly associated with the increase in overall expenditures. Nosocomial infections, on the other hand, 4 folded the overall cost of non-septic counterparts and the increments were significant in overall costs and each sub item.

Neonatal sepsis, which was culture-positive with multidrug resistant organisms has dramatically increased the hospitalization expenditures by \$15,199 (95% CI: 9,450-18,511), in which the nursing or services and pharmaceutical expenses contributed the most. Non-MDRO sepsis also increased the direct medical cost compared to sepsis free neonates, however, the difference in costs was not statistically significant. In addition, MDRO-sepsis was associated with an extension in hospitalization day of 41 (95%CI: 31-50) days. Similarly, there was no significant increase in non-MDRO sepsis group regarding hospital stay. Nevertheless, non-MDRO sepsis has significantly increased the antimicrobial (\$179, 95% CI:117-253), and laboratory testing (\$103, 95% CI:47-177) spending's.

## DISCUSSION

This study sheds light on the clinical and financial costs of healthcare-associated infections in a NICU in Taizhou, Eastern China. Clinicians' understanding of the financial costs associated with newborn sepsis should be created in order to address the significance of hospital infection control and adequate antimicrobial medication usage. Additionally, it is necessary to pay more attention to prolonged NICU stays, catastrophic medical costs brought on by nosocomial infections, and pathogens resistant to antibiotics during health services delivery. Thus, nosocomial infection control is with increasing concern in neonatal wards.

In our study, the incidence of neonatal sepsis was 24 per 1000 NICU admissions, this was slightly lower than the national

incidence 25 per 1000 in 2015. This may suggest that the nosocomial infection control program has improved over the past few years with the enforcement of the prevention and control of nosocomial infections in maternal and child care institutions in 2021. However, the incidence was lowest (21/1000) in 2021 and highest (27/1000) in 2022. This might be because COVID-19 has re-emerged after China terminated its zero-COVID policy.

Based on a 68 hospital study across 7 main regions in China, hospital acquired multidrug resistant organism infections attributable economic loss was \$3853.63.

In Ghana, newborns with Blood Stream Infections (BSI) required 10 more days in the NICU than their non-infected counterparts. Additionally, it was revealed that extremely low birth weight babies had the highest BSI attributable direct cost. The NICU day has grown by 31 days (95% CI: 16-43) as a result of nosocomial sepsis, according to our study. In Greece, neonatal Central-Line Bloodstream Infections (CLBSIs) have added 21 days in hospitalization and €13,727 in medical cost. Despite the significant clinical and economic effects, there is limited information on the cost of HAIs in this area. The estimated financial burden attributed to nosocomial sepsis was \$6,287 (95%CI: 2,372-11,688). The economic loss in the study was considerable larger than in an African scholar, which found the neonatal bloodstream infection contributed to \$334 (US\$ in 2017). It was lower than the findings in western countries. Although CLBSI, a particular kind of hospital-acquired sepsis, had a negative financial impact, the variation in attributable costs may be greatly influenced by monetary inflation and regional healthcare expenditures.

Moreover, the economic losses attributed to MDRO-sepsis acquired in hospital were estimated to be \$15,199, which was 1.17 times of the per capita Gross Domestic Product (GDP) in Taizhou city, China in 2021. Notably, HAI-attributable costs vary due to factors such as geographic regions and the levels of the healthcare facility. Besides, the discrepancy of the estimation was not only affected by the above factors, but also the analytical methods. According to Osborne JW and Overbay A, when normality is violated, parameter or statistics estimation may be challenged by outliers. The financial outcomes and lengths of days presented in inversely Gaussian distribution in our study. As a result, they were analysed and presented in non-parametric statistics. In light of this, comparisons between our findings and those of other researchers need to be made cautiously.

The economic costs related to non-HAI sepsis were not significantly greater than those of non-sepsis controls. However, the costs of treating neonates have significantly escalated due to nosocomial sepsis and MDRO-sepsis. Antimicrobial infections and hospital acquired infections required more health services and diagnostic testing, whereas the pharmaceutical costs were also rising. This indicated that MDRO-sepsis and nosocomial sepsis in neonatal wards required more involved medical care and a longer hospital stay, as well as more complicated treatments. Evidence has shown MDRO-sepsis has deteriorated the prognosis of neonates. The significant fatality and financial consequences associated with MDRO-sepsis indicate that MDRO and hospital acquired infection prevention and control efforts need to be stepped up. Dedicated infection control teams with strict policies and comprehensive tactics should be created in NICUs. Strengthened antimicrobial stewardship, proper bed distance, appropriate surface cleaning, improved hand hygiene practice, timely removal of mechanic devices, sufficient nursing staffing, and separation of MDRO and HAI neonates from the non-infected can all help to limit cross-infection and prevent nosocomial infections.

## **Limitation**

Several additional limitations should be considered in this study. First, while the statistical matching process reduced confounding variables, the covariates included in the Propensity Score Matching (PSM) were only those available in the existing data, potentially affecting the results' validity [20]. Second, we did not identify the adverse effect of prematurity or the

birth weight due to the rare outcome events (either HAI-sepsis or MDRO-sepsis). However, these factors can escalate the financial consequences which should not be overlooked. In our context, occurrences of both nosocomial and MDRO neonatal sepsis were infrequent. Nevertheless, to enhance the study's validity and reliability, it would be beneficial to incorporate longitudinal follow-up and expand the participant pool. While the financial burden was determined based on the overall hospitalization expenditure, a more accurate reflection of the economic loss attributable to healthcare-associated infection may be obtained through a post-infection evaluation. This study was conducted in a single NICU, this can limit the generalization and reliability of the study findings. Additional research, incorporating larger and more diverse samples, is imperative to validate and build upon the results in this study.

## CONCLUSION

In conclusion, benefitting from the statistical matching process, the study provided a precise estimation of financial fallouts of HAI and MDRO neonatal sepsis. The results showed that hospital acquired infections attributable economic loss and prolonged LOS were noticeable pronounced in the NICU at Taizhou Hospital, China. Nosocomial infections also result in significant waste in healthcare resources, such as nursing, laboratory testing, and pharmaceuticals. The significance of preventing and managing nosocomial infections becomes evident in light of these discoveries, as they offer a means to safeguard newborns from contracting infections during their stay in medical facilities. Such measures not only help mitigate the financial strain on patients and the healthcare system but also emphasize the need for proactive infection control in hospitals.

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## POTENTIAL CONFLICTS OF INTEREST

None.

## CONSENT FOR PUBLICATION

Not applicable.

## DATA AVAILABILITY STATEMENT

Due to privacy considerations, the datasets created and/or analyzed during the current work are not publicly available, but they are available to the corresponding author and any related organizations upon justifiable request.

Ethics approval and consent of participants

The research procedures of this study underwent a thorough evaluation and received approval from the ethics committee of the hospital (Approval NO. K20230503). All methodologies employed in the study adhered to the principles outlined in the Helsinki Declaration. Since the data analyzed in this study were anonymized and did not contain any personally identifiable information, obtaining informed consent from the individuals involved was not required.

## COMPETING INTERESTS

All authors declare that they have no conflicts of interest.

## AUTHOR'S CONTRIBUTIONS

XC and TD designed the model and the computational framework and analyzed the data. ZY, LH, and WH carried out the implementation. XC and ZY performed the calculations. XC and LH wrote the manuscript with input from all authors. XC and TD conceived the study and were responsible for the overall direction and planning. All authors read and approved the final manuscript.

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