

Original Article

Risk factors for mortality over 18 years in 317 ICUs in 9 Asian countries: The impact of healthcare-associated infections

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Abstract

Objective: To identify risk factors for mortality in intensive care units (ICUs) in Asia.

Design: Prospective cohort study.

Setting: The study included 317 ICUs of 96 hospitals in 44 cities in 9 countries of Asia: China, India, Malaysia, Mongolia, Nepal, Pakistan, Philippines, Sri Lanka, Thailand, and Vietnam.

Participants: Patients aged >18 years admitted to ICUs.

Results: In total, 157,667 patients were followed during 957,517 patient days, and 8,157 HAIs occurred. In multiple logistic regression, the following variables were associated with an increased mortality risk: central-line-associated bloodstream infection (CLABSI; aOR, 2.36; $P < .0001$), ventilator-associated event (VAE; aOR, 1.51; $P < .0001$), catheter-associated urinary tract infection (CAUTI; aOR, 1.04; $P < .0001$), and female sex (aOR, 1.06; $P < .0001$). Older age increased mortality risk by 1% per year (aOR, 1.01; $P < .0001$). Length of stay (LOS) increased mortality risk by 1% per bed day (aOR, 1.01; $P < .0001$). Central-line days increased mortality risk by 2% per central-line day (aOR, 1.02; $P < .0001$). Urinary catheter days increased mortality risk by 4% per urinary catheter day (aOR, 1.04; $P < .0001$). The highest mortality risks were associated with mechanical ventilation utilization ratio (aOR, 12.48; $P < .0001$), upper middle-income country (aOR, 1.09; $P = .033$), surgical hospitalization (aOR, 2.17; $P < .0001$), pediatric oncology ICU (aOR, 9.90; $P < .0001$), and adult oncology ICU (aOR, 4.52; $P < .0001$). Patients at university hospitals had the lowest mortality risk (aOR, 0.61; $P < .0001$).

Conclusions: Some variables associated with an increased mortality risk are unlikely to change, such as age, sex, national economy, hospitalization type, and ICU type. Some other variables can be modified, such as LOS, central-line use, urinary catheter use, and mechanical ventilation as well as and acquisition of CLABSI, VAE, or CAUTI. To reduce mortality risk, we shall focus on strategies to reduce LOS; strategies to reduce central-line, urinary catheter, and mechanical ventilation use; and HAI prevention recommendations.

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The goals of medicine include alleviating pain and suffering, promoting health, preventing disease and death, achieving a peaceful death, curing disease when possible, and caring for patients for whom there is no cure.¹ The International Nosocomial Infection



Control Consortium (INICC) is aligned with these objectives through the surveillance and prevention of healthcare-associated infections (HAIs).² The INICC is the first and largest multinational HAI surveillance, prevention, and investigation network, and it has operated internationally since 2002.³ The INICC has been publishing international reports that provide data on HAI rates and related mortality. Its first report was in 2006,⁴ and subsequent reports were published in 2008,⁵ 2010,⁶ 2012,⁷ 2014,⁸ 2016,⁹ 2019,¹⁰ and 2021.¹¹

In addition, an INICC investigation showed that patients without an HAI have a mortality rate of 17%, whereas those with 1 HAI have a mortality rate of 30%–48% and patients with 3 HAIs have a mortality rate of 63%.¹¹

In multivariate logistic regression analysis, ICU-acquired infection remained an independent risk factor for hospital mortality after adjustment for APACHE II score and age.¹²

In a study analyzing clinical outcomes and risk factors for mortality from ventilator-associated events of patients hospitalized in ICU, older age, higher APACHE II score on ICU admission, blood transfusion, immunosuppressive drugs, and presence of a central line were associated with higher risks for all-cause mortality in an ICU.¹³ In a study of risk factors for long-term mortality of critically ill elderly patients admitted to an ICU, in-hospital mortality risk was independently associated with mechanical ventilation, use of vasopressors, and neurological disease.¹⁴

These studies have analyzed the impact of severity of illness scores, underlying disease, age, sex, presence of HAI, and a few other variables. However, no study has included multiple nations on multiple continents simultaneously, and no study has been conducted prospectively over 18 years. Furthermore, no other study has examined the following factors and their association with mortality: income per country (ie, low, lower-middle, upper-middle, and high income), hospital ownership (ie, private, public, university, and nonprofit), type of hospitalization (medical or surgical), ICU type (ie, cardiothoracic, coronary, medical, medical-surgical, neurosurgical, neurologic, adult oncology, pediatric oncology, pediatric, respiratory, surgical, trauma, and burn), device days (ie, central-line days, mechanical ventilation days, and urinary catheter days), device utilization ratio (ie, central-line usage, mechanical ventilation, and urinary catheter usage). We analyzed the impact of these variables and others on risk of mortality.

Methods

Study population and design

This multicenter, multinational, cohort, prospective study was carried out with patients admitted to 317 ICUs from 96 hospitals in 44 cities in 9 Asian countries over 18 years between March 27, 2004, and February 11, 2022.

Surveillance of healthcare-associated infections

The data were collected on each patient at the time of their ICU admission. From admission to discharge, infection prevention professionals (IPPs) went to the bedside of each patient daily. All adult and pediatric patients with or without HAIs admitted to an ICU were prospectively included in this investigation, and their data were collected from admission to discharge using the INICC Surveillance Online System (ISOS).^{2,3} IPPs visit the bedside of each hospitalized patient in the ICU with a computer tablet; they log into the ISOS and upload the patient's data in real time.^{2,3}

At the time the patient is admitted, details about the setting (ie, country, city, hospital name, and type of ICU) are uploaded. Patient details are also input, including type of hospitalization (surgical or medical), use of invasive devices (central line, mechanical ventilator, urinary catheter, and/or peripheral catheter), and presence of infection.^{2,3} IPPs further upload information about invasive devices (ie, central line, mechanical ventilator, urinary catheter, and/or peripheral catheter), positive cultures (ie, blood cultures, urine cultures, and respiratory samples), and medications every day until the patient is released.^{2,3}

If the patient has signs or symptoms of infection, an infectious disease specialist approaches the patient to determine the presence of an HAI (CLABSI, VAE, CAUTI, or other). According to the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN), IPPs look at a patient's signs and symptoms, cultures, radiographs, and other described criteria to fulfill definitions of HAI.^{15,16} When IPPs upload the result of a culture to the ISOS, the ISOS immediately shows a message to the IPP and leads the IPP to an online module of the ISOS to check all the criteria of CDC NHSN to confirm the presence of an HAI and kind of HAI (CLABSI, VAE, CAUTI, or other).^{2,3}

The ISOS automatically checks device utilization daily. From admission to discharge, the ISOS sends messages to the IPPs when a bias on bed days or use of devices is detected. If ISOS detects lack of use of any kind of device on any given day, it will send a message to IPP to remind him or her to upload missing devices or upload the discharge of the patient. If the patient is hospitalized in an ICU without any device in place, it is most probably because the IPP forgot to upload the use of the devices to the ISOS or forgot to upload the patient's discharge. Thus, the ISOS requests that IPPs investigate why a patient in an ICU has no device in place.^{2,3} This approach significantly reduces biases associated with device utilization, bed days, and discharge conditions.^{2,3}

Patients with missing data for their age or sex were excluded from this analysis. This study was approved by the institutional review boards of the hospitals involved. The identities of patients and hospitals are confidential.

Recorded data

Income group by World Bank (low, lower-middle, upper-middle, or high income), country name, city name, hospital name, hospital ownership (public, university, private, or nonprofit), ICU type, age, sex, device utilization (central-line days, mechanical ventilation days, urinary catheter days, central-line utilization ratio, mechanical ventilation utilization ratio, and/or urinary catheter utilization ratio), bed days, cultures, presence of HAI (CLABSI, VAE, or CAUTI), and clinical outcome at discharge (dead or alive) were recorded. The treatment outcome of HAIs was evaluated as discharge all-cause mortality.

INICC surveillance online system

According to standard CDC/NHSN methods, HAI numerators and denominators are device days collected from all patients as pooled data without specifying patient characteristics or the number of device days related to each patient.^{15,16}

INICC HAI surveillance is carried out using an online platform, the ISOS, which includes CDC/NHSN criteria and methods.^{15,16} ISOS also adds the collection of patient-specific data on all patients, with and without HAI, including their risk factors and other variables per patient.^{2,3}

Data from all patients admitted to the ICU, infected or uninfected, allowed matching by various characteristics, which facilitated the estimation of risk factors for HAIs and mortality. Data were collected through the INICC ISOS, and the latest CDC/NHSN criteria and methodology were applied to diagnose HAIs, calculate HAI rates, and calculate device utilization ratio, among other variables.^{15,16} Definitions of HAI used during surveillance were those published by CDC in 1991¹⁵ and their subsequent updates through 2017.¹⁶

Statistical analysis

Surviving and deceased patients were compared using multiple logistic regression. Independent variables are included in Table 2. Statistically significant variables were associated with an increased mortality risk. The test statistic used was the Wald test, and the statistical significance level was set at 0.05. Calculated using the outputs of logistic regression, adjusted odds ratios (aORs), and the corresponding 95% confidence intervals (CIs) of statistically significant variables were also reported. We estimated variables independently associated with the outcome adjusted to confounders. All statistical analyses were performed using R version 4.1.3 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

From March 27, 2004, through February 11, 2022, a course of 18 years, a cohort, prospective, multicenter surveillance study of HAIs was conducted in 317 ICUs of 96 hospitals in 44 cities in 9 countries from Asia (China, India, Malaysia, Mongolia, Nepal, Pakistan, Philippines, Sri Lanka, Thailand, and Vietnam) currently participating in the INICC. Of all 96 hospitals, 20 (20.8%) were academic, 23 (23.9%) were public, 49 (51.1%) were private, and the remaining 4 (4.2%) were philanthropic. Among all 317 ICUs, 78 (24.6%) were medical-surgical, 59 (18.6%) were medical, 28 (8.8%) were pediatric, 34 (11.7%) were surgical, 29 (9.2%) were coronary, 16 (5.1%) were neurologic, 27 (8.5%) were neurosurgical. In addition, 7 ICUs (2.2%) were trauma units, and 10 ICUs (2.5%) were respiratory units. Furthermore, 5 ICUs (1.6%) were oncology pediatric ICUs, 13 (4.1%) were cardiothoracic ICUs, 5 (1.6%) were oncology adult ICUs, and 9 (9.2%) were burn units.

The length of participation of hospitals in INICC ranged from 1.23 to 201.93 months (mean, 40.50; SD, 41.31). More participating hospitals and patient characteristics are shown in Table 1. Data on 157,667 critical patients were gathered, and these patients were followed from admission to discharge from ICU during 957,517 bed days, and they acquired 8,157 HAIs. The mortality rate for patients at adult oncology ICUs was 29%. At medical ICUs, the mortality rate was 13%; at surgical ICUs, the mortality rate was 7%; at pediatric ICUs, the mortality rate was 7%, and at coronary ICUs, the mortality rate was 6%.

Using multiple logistic regression, we identified the following variables as statistically significantly independently associated with a higher risk of mortality (Table 2): Acquisition of a CLABSI (aOR: 2.36; $P < .0001$), VAE (aOR, 1.51; $P < .0001$), or CAUTI (aOR, 1.04; $P < .0001$) was associated with higher mortality risk. Female sex had a higher mortality risk than male sex (aOR, 1.06; $P < .0001$). Older age (aOR, 1.01; $P < .0001$) increased mortality risk by 1% per year. More bed days (aOR, 1.01; $P < .0001$) increased mortality risk by 1% per bed day. More central-line days (aOR, 1.02; $P < .0001$) increased mortality risk by 2% per central-line day. More urinary catheter days (aOR, 1.04; $P < .0001$) increased mortality risk by 4%

per urinary catheter day. Higher mechanical ventilation utilization ratio (aOR, 12.48; $P < .0001$) increased mortality risk. Upper-middle income country was associated with higher mortality risk (aOR, 1.09; $P = .033$). The variables with the highest mortality risk were surgical hospitalization (aOR, 2.17; $P < .0001$), pediatric oncology ICU stay (aOR, 9.90; $P < .0001$), and adult oncology ICU stay (aOR, 4.52; $P < .0001$). Meanwhile, surgical ICU stay (aOR, 0.43; $P = .01$), cardiothoracic ICU stay (aOR, 0.41; $P = .01$), and surgical ICU stay (aOR, 0.24; $P < .0001$) showed the lowest mortality risks. Compared with public, private, and nonprofit hospitals, patients at university hospitals had the lowest mortality risk (aOR, 0.61; $P < .0001$).

Discussion

In this study, CLABSI, VAE, CAUTI, age, sex, length of stay, mechanical ventilation utilization ratio, central-line days, urinary catheter days, upper-middle income countries, surgical hospitalization, and oncology ICU were identified associated with an increased mortality risk. The associations between CLABSI, VAE, and CAUTI and increased mortality risk in our study are consistent with findings of Toufen et al,¹⁷ in which mortality risk was independently associated with nosocomial infection in patients in the surgical ICU.

Older age was also associated with increased mortality risk in our study. We observed a 1% increase in mortality risk per year of age. Similarly, in a study at an ICU in northern Thailand, age was a risk factor for mortality.¹⁸ Additionally, we identified an association between female sex and mortality risk in our study. Conversely, in an ICU in southern India, male sex had a higher mortality risk.¹⁹

Moreover, we detected an association between prolonged length of stay and mortality, which is consistent with a previous study that analyzed risk factors for mortality in VAE in ICU patients in which prolonged hospital stay was an independent risk factor for mortality in multivariate analysis.²⁰

Furthermore, we identified an association between invasive mechanical ventilation utilization ratio and increased mortality risk. This finding is consistent with the findings of Toufen et al,¹⁷ in which mortality was independently associated with the need for mechanical ventilation among patients in the surgical ICU.

Furthermore, we observed an association between central-line days and mortality. We detected a 2% increase in mortality risk per day of use of a central line. A similar association was shown in a study at a surgical ICU that analyzed risk factors and mortality of patients with intravenous catheter-related bloodstream infections. In that study, in multivariable analyses, catheterization of patients in the general wards was the sole independent risk factor of CRBSI occurrence (OR, = 8.67; $P < .01$) and males (OR, 7.20; $P = .03$) had the highest mortality risk.²¹

In this study, we further detected an association between urinary catheter days and increased mortality risk, with a 4% increased mortality per day of urinary catheter use. No other study has reported this association.

In the current study, patients in university hospitals had a significantly lower mortality risk than patients in private or public hospitals. Regarding this association, Eggleston et al²² conducted a systematic review to analyze factors that explain the diversity of findings associated with the ownership and quality of hospitals. Government-controlled, for-profit hospitals had higher mortality rates than nonprofit hospitals.²² Devereaux et al²³ conducted a

Table 1. Setting and Patient Characteristics

Variable	Total
Period	2004-03-27 to 2022-02-11
Years, no.	18
ICUs, no.	317
Hospitals, no. (%)	96
Cities, no. (%)	44
Countries, no.(%)	9
Total patients, no. (%)	157,667
Survival status, no. (%)	
Alive	140,431 (89.1)
Death	17,236 (10.9)
Income per country, no. (%)	
Lower middle	6 (66.7)
Upper middle	3 (33.3)
Patients admitted to hospitals, no. (%)	
Private hospitals	77,835 (49.4)
Public hospitals	17,095 (10.8)
University hospitals	51,593 (32.7)
Charity hospitals	11,144 (7.1)
Patients with medical hospitalization, no. (%)	118,964 (75.5)
Patients with surgical hospitalization, no. (%)	38,703 (24.6)
Patients admitted to ICU, no. (%)	
Cardio-thoracic ICU	4,366 (2.8)
Coronary ICU	10,045 (6.4)
Medical ICU	25,492 (16.2)
Medical-surgical ICU	91,844 (58.3)
Neuro-surgical ICU	5,054 (3.2)
Neurologic ICU	1,487 (0.1)
Adult oncology ICU	52 (0.03)
Pediatric oncology ICU	20 (0.01)
Pediatric ICU	6,709 (4.3)
Respiratory ICU	60 (0.03)
Surgical ICU	9,866 (6.3)
Trauma ICU	2,508 (1.6)
Burn ICU	164 (0.1)
Sex, no. (%)	
Male	99,568 (63.2)
Female	58,099 (36.8)
Age, mean y (SD)	53.68 (21.84)
Central-line days, no., mean d (SD)	717,213; mean, 4.55 (10.56)
Mechanical ventilation days, no., mean d (SD)	288,125; mean, 1.83 (4.73)
Urinary catheter days, no., mean d (SD)	583,944; mean, 3.70 (5.37)
Central-line utilization ratio, mean (SD)	0.74; mean, 4.02
Mechanical ventilation utilization ratio, mean (SD)	0.30
Urinary catheter, utilization ratio, mean (SD)	0.60
Patient days, no.	957,517

(Continued)

Table 1. (Continued)

Variable	Total
Average LOS, mean d (SD)	6.07 (7.45)
CLABSI, no. (%)	2,453 (30.1)
VAE, no. (%)	4,260 (52.2)
CAUTI, no. (%)	1,444 (17.7)

Note. ICU, intensive care unit; LOS, length of stay; CLABSI, central-line-associated bloodstream infection; VAE, ventilator-associated events; CAUTI, catheter associated urinary tract infection; SD, standard deviation.

Table 2. Multiple Logistic Regression Analysis of Risk Factors Associated With Death

Variable	aOR	95% CI	P Value
CLABSI	2.36	2.14–2.61	<.0001
VAE	1.51	1.41–1.55	<.0001
CAUTI	1.04	0.90–1.21	<.0001
Age	1.01	1.01–1.02	<.0001
Sex, female	1.06	1.02–1.10	<.0001
Length of stay	1.01	1.01–1.02	<.0001
Mechanical ventilation utilization ratio	12.48	11.73–13.28	<.0001
Central-line utilization ratio	0.95	0.93–0.97	<.0001
Urinary catheter utilization ratio	0.91	0.87–0.96	<.0001
Central line days	1.02	1.02–1.03	<.0001
Mechanical ventilation days	0.95	0.94–0.95	<.0001
Urinary catheter days	1.04	1.03–1.04	<.0001
Private hospitals	0.89	0.82–0.96	<.0001
Public hospitals	0.75	0.68–0.82	<.0001
University hospitals	0.61	0.57–0.67	<.0001
Income per country, upper middle	1.09	1.01–1.18	.033
Surgical hospitalization	2.17	2.04–2.27	<.0001
Pediatric oncology ICU	9.90	3.19–30.69	<.0001
Adult oncology ICU	4.52	1.87–10.93	<.0001
Trauma ICU	1.03	0.52–2.03	.93
Medical–Surgical ICU	0.92	0.47–1.79	.80
Medical ICU	0.85	0.44–1.65	.63
Neurosurgical ICU	0.73	0.37–1.42	.35
Pediatric ICU	0.61	0.31–1.19	.15
Neurologic ICU	0.50	0.25–0.99	.05
Respiratory ICU	0.44	0.16–1.22	.11
Surgical ICU	0.43	0.22–0.85	.01
Cardiothoracic ICU	0.41	0.21–0.81	.01
Coronary ICU	0.24	0.12–0.48	<.0001

Note. aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; CLABSI, central-line-associated bloodstream infection; VAE, ventilator-associated event; CAUTI, catheter-associated urinary tract infection.

systematic review and meta-analysis of studies to compare the mortality rates of private for-profit hospitals with those of and private nonprofit hospitals. They calculated the relative mortality risk of patients in private for-profit hospitals and compared it with the

mortality risk for patients in private nonprofit hospitals. In this adult population, private for-profit hospitals were associated with an increased mortality risk compared to privately owned nonprofit hospitals.^{2,3}

Additionally, patients in upper middle-income countries had a higher mortality risk than patients in lower middle-income countries. This finding can probably be explained by the inadequate quality of healthcare programs in the upper middle-income countries that participated in this study. Surgical hospitalization was associated with a significantly increased mortality risk than medical hospitalization in our study. To our knowledge, no other studies have analyzed this variable. Finally, patients admitted to oncology ICUs had the highest mortality risk, whereas patients admitted to coronary ICU had a significantly lower mortality risk. To our knowledge, this variable has not been analyzed in other research.

Some of the mortality risk factors identified in our study are unlikely to change, such as age, sex, the national economy, medical or surgical hospitalization, and type of ICU. However, some risk factors for death can be modified, such as length of stay, use of a central line, use of a urinary catheter, use of a mechanical ventilator, and acquisition of CLABSI, VAE, or CAUTI. As INICC data have already shown, HAI rates in low- and middle-income countries are 3–5 times higher than in the United States; therefore, there is room for improvement. Our recommendation for reducing mortality risk in ICUs is to focus on strategies to reduce length of stay, strategies to reduce utilization of mechanical ventilator, central lines, and urinary catheters, and to apply an evidence-based set of recommendation to prevent HAIs, such as those recently published by the Society for Healthcare Epidemiologists of America (SHEA), the Infections Diseases Society of America (IDSA), and the Association for Professionals in Infection Control and Epidemiology (APIC).^{24,25}

This study had several limitations. This study is not representative of all hospitals of Asia because it relied on a surveillance system that included hospitals participating voluntarily. The hospitals that participate in this system are likely those with a better-quality program and surveillance and prevention of HAIs. Therefore, the rates of HAI shown in this study may be lower than the actual rates found worldwide. Lastly, data regarding the severity of illness score and underlying diseases were not collected, which may have contributed to identifying them as another mortality risk factor.

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