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# Persistent Mortality Risk From Device-related Healthcare-associated Infection in Kidney Transplant Recipients Despite Multifaceted Interventions Action Calls for a Zero-tolerance Policy

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**Background.** Although multifaceted control intervention actions (bundles) are highly effective in reducing the risk of device-related healthcare-associated infections (d-HAIs), no studies have explored their impact on the outcomes of kidney transplant recipients (KTRs) or the extent of risk reduction achievable through the bundle implementation. **Methods.** Seven hundred ninety-eight prevalent KTRs admitted to the intensive care unit (ICU) requiring invasive devices were included: 449 patients from the bundle preimplementation period and 349 from the postimplementation period. The primary outcome was mortality within 90 d of ICU admission. Using Poisson regression models, the magnitude of risk reduction for d-HAIs after the bundle implementation and the impact of d-HAIs on the risk of death was estimated. **Results.** The 90-d survival rate was significantly lower in patients with d-HAIs (37.7% versus 71.7%; $P < 0.001$). The bundle implementation reduced the risk of d-HAIs by 58% (relative risk, 0.42; $P = 0.005$). Despite the significant reduction in d-HAIs after the bundle implementation, d-HAIs were associated with a 2.6-fold higher risk of death (hazard ratio [HR], 2.63; $P < 0.001$) regardless of the study period. Additional variables associated with increased risk of death included age (HR, 1.03; $P < 0.001$), baseline immunosuppression (HR based on mycophenolate versus others 0.74; $P = 0.02$), time since transplantation (HR, 1.003; $P < 0.001$), platelet count at ICU admission (HR, 0.998; $P < 0.001$), and sepsis as the reason for ICU admission (HR, 1.67; $P < 0.001$). **Conclusions.** The persistent risk associated with d-HAIs, despite the implementation of multifaceted control intervention actions in an ICU specialized in KTR care, underscores the need for a zero-tolerance policy toward d-HAIs.

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Healthcare-associated infections (HAIs) are one of the most critical public health problems to be faced in recent eras.[1] According to World Health Organization estimates, 7 of every 100 patients admitted to intensive care units (ICUs) in high-income countries acquire HAIs, whereas in low- and middle-income countries, this ratio increases to 16–37 patients.[1,2] These numbers are even higher in patients who require invasive devices such as central venous catheters (CVCs), urinary catheters (UCs), or mechanical ventilation (MV).[3-6] The impacts of each HAI, and mainly those related to invasive devices (d-HAIs), are dramatic, resulting in increased hospital stays, with consequences for the overall health of vulnerable patients, increased need for advanced life support resources, and higher costs and risk of death.[7]

Implementing multifaceted control intervention actions (bundles of HAI prevention) significantly reduces the occurrence of HAIs.[8-10] Previous studies demonstrate a 35% to 60% reduction when these intervention bundles are implemented, regardless of each country's income level.[10] Much of the evidence evaluates the overall impact of these measures, occasionally breaking down the results by levels of care, such as for patients in ICU care, specific sites of HAI, or if associated or not associated with invasive devices.[11-13] However, analyses

in subpopulations of patients who could be considered more vulnerable to infectious conditions and more severe outcomes, such as kidney transplant recipients (KTRs), are scarce.

Kidney transplantation is the preferred renal replacement therapy (RRT) for patients with advanced chronic kidney disease (CKD).[14] Despite better outcomes when compared with other RRT modalities,[15-17] KTRs have high incidences of infectious and cardiovascular events,[18-21] which can evolve into more severe conditions, requiring advanced life care in ICUs where they are inevitably exposed to the use of invasive devices. To date, no studies have explored the impact of HAIs on the outcomes of KTRs and the magnitude of risk reduction when preventive measures are adopted. In this study, we evaluated the impact of d-HAIs on the risk of death in ICU-admitted KTRs. We demonstrated that even with the significant reduction in d-HAI occurrence with the adoption of bundles of prevention, their occurrence poses a significant risk of death, justifying the implementation of zero-tolerance policies toward HAIs.

## MATERIALS AND METHODS

### Design

This retrospective cohort study included prevalent KTRs under follow-up at Hospital do Rim, Fundação Oswaldo Ramos, admitted to the ICU between March 2016 and June 2019. In December 2017, in collaboration with the Brazilian Ministry of Health, the ICU of Hospital do Rim completed the implementation phase of multifaceted control intervention actions for HAI prevention, which are designated bundles for HAI prevention, detailed in **Tables S1–S3** (**SDC,** http://links.lww.com/TXD/A732). Due to a change in care routine after December 2017 (bundles fully implemented), with 2 distinct periods, a natural before-and-after experiment was designed. The observation period was concluded up to 90 d after ICU admission. The study was approved by the Institutional Review Board of the Federal University of São Paulo, approval number 4.228.520, with a waiver for the application of the informed consent form.

### The Study Site

Hospital do Rim is a tertiary hospital located in São Paulo, Brazil, dedicated to kidney transplants with 151 beds, including a 16-bed ICU. Since its inception in 1998, the Center has performed almost 1000 kidney transplants yearly, 85% from deceased donors, and is supported by the Brazilian Public Health System. As of June 2019, the Center had 11 875 KTRs on follow-up in the local outpatient clinic. The Center has a specific 8-bed unit for postoperative intermediate management. As a consequence, the recipients in the immediate postoperative period are not transferred to the ICU, only in cases where the recipients are hemodynamically unstable or have high cardiovascular risk.

### Inclusion and Exclusion Criteria

Only adult KTRs (age 18 y or older) prevalent in the transplant program of Hospital do Rim who were admitted to the ICU were eligible for the study. The observation period spanned 90 d, during which any ICU readmissions were not treated as new entries; each readmission was recorded as a clinical event. Recipients in the immediate postoperative period of kidney transplantation were not included, as the study aimed to investigate outcomes in patients who had undergone immunosuppression. Additionally, as mentioned previously, the Center has a dedicated unit for the immediate postoperative recovery of KTRs, which is separate from the ICU.

The natural intervention started in December 2017, but a total adaptation period of 6 mo was considered: 3 mo before December 2017 (training time) and 3 mo after (adaptation time). Therefore, patients admitted 3 mo before and 3 mo after December 2017 were not considered for inclusion. Furthermore, because the study aimed to evaluate only HAIs associated with the 3 devices—CVC, UC, and MV—patients who did not use any of these devices were also excluded. Patients who received combined or sequential transplants with another solid organ, those who experienced graft loss before ICU admission, and those who were transferred from other hospital units were excluded because of the possibility of already being in use of devices, with or without the application of the bundles in question.

### Multifaceted Control Interventions Actions

The multifaceted control interventions targeted all types of HAIs, but we detailed the bundles specifically related to d-HAIs for this analysis. After the recommendations of the Institute for Healthcare Improvement and the Centers for Disease Control and Prevention, the program also adheres to guidelines from the Brazilian Health Regulatory Agency (ANVISA). Although various types of HAIs were addressed, this analysis focuses on d-HAIs, specifically central line-associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), and ventilator-associated pneumonia (VAP). **Tables S1–S3** (**SDC,** http://links.lww.com/TXD/A732) provide further details on these control interventions.

In brief, the CLABSI bundle included measures for initial preparation, insertion, maintenance, dressing, and timely catheter removal decisions. For CAUTIs, the bundle covered best practices for insertion and maintenance. The VAP bundle included general preventive measures, ventilator care, and humidifier management.

### Variables of Interest

The variables of interest were collected from the institution databases or patient medical records and included in Research Electronic Data Capture, where patients were anonymized and de-identified. These variables were grouped into demographic characteristics, ICU admission details, events after ICU admission, and device usage. The first group included the age at ICU admission, sex, ethnicity, cause of CKD, type of donor, posttransplant diabetes, Charlson Comorbidities Index, and baseline immunosuppression. The ICU admission variables were time since transplantation, the reason for admission, Sequential Sepsis-related Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score III (SAPS III) indexes, estimated glomerular filtration rate (eGFR, estimated by Chronic Kidney Disease Epidemiology Collaboration equation),[22] hemoglobin, and platelets count. The events after ICU admission were the use of vasopressor, acute kidney injury (AKI, according to Kidney Disease Improvement Global Outcome definition),[23] and RRT requirement. Finally, as mentioned before, the 3 devices considered were CVC, UC, and MV.

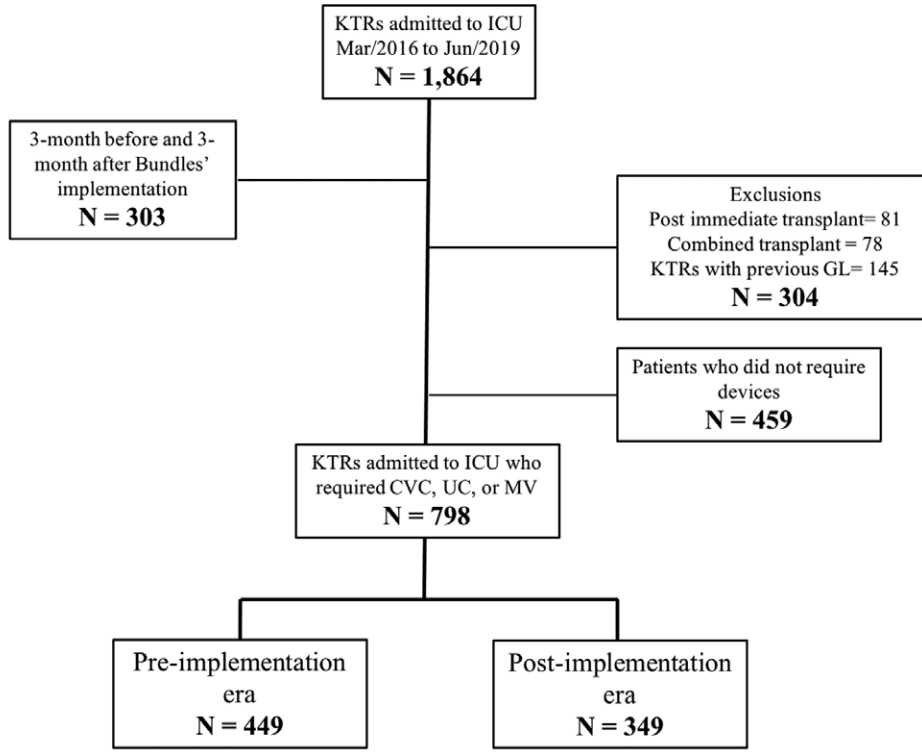


**FIGURE 1.** Population disposition. CVC, central venous catheter; GL, graft loss; ICU, intensive care unit; KTR, kidney transplant recipient; MV, mechanical ventilation; UC, urinary catheter,

## Outcomes

The primary outcome was death within 90 d of ICU admission. Secondary outcomes were the incidence of d-HAI cases, which were considered grouped or each one separately: CLABSI, CAUTI, and VAP. HAIs were defined according to the Institute for Healthcare Improvement and the periodic guidelines set by the Brazilian Health Regulatory Agency (ANVISA).[24] These criteria are detailed in the supplementary material (**Table S4, SDC,** http://links.lww.com/TXD/A732).

## Statistical Analyses

Numerical variables were evaluated for normality using the Kolmogorov-Smirnov test, and because none of them showed a normal distribution, all were summarized by median and interquartile range (IQR). Absolute numbers and percentages summarized categorical variables. Initially, the population was stratified according to the eras (before-and-after intervention), and numerical variables were compared using the nonparametric Mann-Whitney test, whereas categorical variables were compared using the $\chi^2$ test or Fisher exact test. This same strategy was used to compare variables when the populations were stratified by the occurrence or not of d-HAIs or the occurrence or not of death.

Because all included patients used at least one of the invasive devices considered for analysis, d-HAIs were counted on the basis of the incidence of cases. The incidence was calculated as the ratio of d-HAIs (grouped or by device) to the number of exposed patients. A multivariable analysis was performed using Poisson regression with robust effects to estimate the impact of the intervention (bundle implementation) on the risk of HAIs. Only variables that achieved a $P$ value of <0.10 (arbitrarily defined) in univariate comparisons between patients with and without d-HAIs, excluding collinearities, were included in the multivariable model.

The primary outcome (death within 90 d) was evaluated using the Kaplan-Meier method and compared with the occurrence of d-HAIs using the log-rank test. The impact on the risk of death was firstly estimated by the relative risk (RR) of death in patients with d-HAIs in each era (before and after intervention). Subsequently, a multivariate analysis was performed using a Poisson model, considering the exposure time. Variables included in the model were those that achieved a $P$ value of <0.10 (arbitrarily defined) in the univariable analysis comparing patients who died with those who did not. The d-HAIs were included as a predictor variable, and the model was estimated using generalized structural equation modeling.

All analyses were performed using SPSS software version 28 (SPSS Inc, Chicago, IL), and the generalized structural equation model was performed using STATA. A $P$ value of <0.05 was considered statistically significant for a 95% confidence interval (CI).

# RESULTS

Between March 2017 and June 2019, 1864 KTRs were admitted to the ICU. Of these, 607 were excluded on the basis of criteria detailed in Figure 1, and 459 were excluded from this analysis because they did not require invasive devices during their ICU stay. Therefore, 798 patients were included in this analysis.

### Demographic Characteristics

The patients were aged 58.0 y, 59.3% were men, and 62.4% were White. The average time from kidney transplant to ICU admission was 58.9 mo. Most patients were receiving calcineurin inhibitors (CNIs) and prednisone, combined with either mycophenolate (46.6%) or azathioprine (25.9%), as part of their maintenance immunosuppressive regimen. The mean Charlson Comorbidity Index was 5.0. The primary reasons for ICU admission were sepsis (25.2%), postoperative care unrelated to kidney transplant management (19.9%), acute respiratory failure (16.8%), and neurological disorders (12.5%). Upon ICU admission, the mean SOFA score was 6.0, and the SAPS III was 52.0. These demographic characteristics are detailed in Table 1.

During their ICU stay, 77.3% of patients had AKI, 49.1% required RRT, and 49.7% had vasopressors. Regarding device usage, 82.3% had CVC, 70.0% had UC, and 45.5% required MV.

### Comparison Between Eras

Comparing the patients in both periods (Table 1), those in the postimplementation period were less likely to be recipients of kidneys from deceased donors (72.8% versus 80.6%, $P = 0.009$), had a longer time since transplantation (65.2 versus 47.0 mo, $P = 0.001$), and tended to be less frequently receiving CNI combined with mycophenolate (43.3% versus 49.2%, $P = 0.07$). The SOFA scores (5.0 versus 6.0 points, $P = 0.001$) and incidence of AKI (73.9% versus 80.0%, $P = 0.04$) were lower in the postimplementation period, whereas the rates of vasopressor use (49.3% versus 50.1%, $P = 0.82$) and RRT requirement (47.9% versus 50.1%, $P = 0.53$) were similar in both periods. There were no significant differences in the rates of MV (47.6% versus 43.7%, $P = 0.27$) or UC use (69.1% versus 71.9%, $P = 0.37$), but CVC usage was significantly higher in the postimplementation period (87.1% versus 78.6%, $P = 0.002$).

### Device-related HAIs

The overall rate of d-HAIs was 6.6%, with 6.4% for CLABSI, 1.05% for CAUTI, and 1.38% for VAP (Table 1). The incidence of d-HAIs was significantly lower in the postimplementation period (4.0% versus 8.7%, $P = 0.009$), primarily due to reduced CLABSI rates (3.9% versus 8.5%, $P = 0.017$). Although there were numerical reductions in CAUTI (0.4% versus 1.5%, $P = 0.34$) and VAP (0.6% versus 2.0%, $P = 0.38$), these differences were not statistically significant.

### Variables Associated With d-HAIs

When comparing KTRs based on the occurrence of d-HAIs (**Table S5, SDC,** http://links.lww.com/TXD/A732), those with d-HAIs were more frequently admitted to the ICU due to acute respiratory failure (28.3% versus 16.0%) or neurological disorders (24.5% versus 11.7%, $P = 0.005$) and had lower platelet counts (144 versus 155 × 1000 cells/mm$^3$, $P = 0.02$). They also tended to have a longer time since transplantation (87.9 versus 58.0 mo, $P = 0.09$) and a higher eGFR at ICU admission (24.8 versus 19.6 mL/min/1.73 m$^2$, $P = 0.05$). The following variables were included in the Poisson model for the probability of d-HAIs: reason for ICU admission (categorized in sepsis versus others); Charlson Comorbidity Index (for each point); time after transplantation (for each month); hemoglobin (for each 1 g/dL), platelets (for every 1000 cells/mm$^3$), and eGFR (for each 1 mL/min) at ICU admission; and the era (post- versus preimplementation). The Poisson model results are shown in Table 2. Bundle implementation independently reduced the risk of d-HAIs by 58% (RR, 0.42; 95% CI, 0.23-0.77; $P = 0.005$). Other variables associated with d-HAIs included hemoglobin levels (RR for each g/dL increase, 0.89; $P = 0.03$), platelet count (RR for 1000 cells/mm$^3$ increase, 0.99; $P = 0.03$), and eGFR (RR for each mL/min increase, 1.01; $P = 0.02$), all at ICU admission.

### The Impact of d-HAIs on the Risk of Death

The median ICU stay was 25.0 d (IQR, 15.0–36.5) for KTRs with d-HAIs and for those without d-HAIs was 5.0 d (IQR, 2.0–10.0; $P < 0.001$). The 30- and 90-d survival rates were significantly lower in KTRs with d-HAIs (58.5% versus 76.4% and 37.7% versus 71.7%, respectively, $P < 0.001$; Figure 2). The median time for death was 11.0 d (IQR, 4.0–26.0) after ICU admission. A total of 244 KTRs died, 124 in the preimplementation and 120 in the postimplementation period. In the first period, the risk of death was 2.39-fold higher for patients who had HAIs (RR, 2.39; 95% CI, 1.70-3.17; $P < 0.001$). Although there was a significant reduction in the incidence of d-HAIs in the second period, when any d-HAI occurred, the risk of death was maintained (RR, 2.17; 95% CI, 1.35-2.88; $P = 0.007$). The patient's survivals according to d-HAIs stratified by era (pre- and postimplementation) are shown in **Figure S1** (**SDC,** http://links.lww.com/TXD/A732). The median hospital stay from ICU admission to discharge was 39.0 d (IQR, 11.0–63.2) for those with d-HAIs, compared with 14.0 d (IQR, 8.0–24.0) for those without d-HAIs ($P < 0.001$).

Comparing survivors and nonsurvivors (**Table S6, SDC,** http://links.lww.com/TXD/A732), those who died were older (62.0 versus 56.0 y, $P < 0.001$), had a higher Charlson Comorbidity Index (6.0 versus 5.0, $P < 0.001$), and had a longer time from transplant to ICU admission (86.7 versus 38.6 mo, $P < 0.001$). Nonsurvivors also had a higher incidence of sepsis at ICU admission (32.4% versus 22.0%, $P < 0.001$), higher SOFA (8.0 versus 5.0, $P < 0.001$), and SAPS III (59.0 versus 49.0, $P < 0.001$) scores. As expected, the rates of vasopressor use (85.2% versus 34.1%, $P < 0.001$), MV (81.6% versus 29.4%, $P < 0.001$), and RRT (63.5% versus 42.8%, $P < 0.001$) were significantly higher among nonsurvivors. The incidence of d-HAIs was also higher among nonsurvivors (13.5% versus 3.6%, $P < 0.001$), notably CLABSI (11.9% versus 3.3%, $P < 0.001$).

In the Poisson model (Table 3), the risk of death was 2.6-fold higher in KTRs with d-HAIs (hazard ratio [HR], 2.63; 95% CI, 1.80-3.84; $P < 0.001$). Other variables associated with increased risk of death included age (HR for each year, 1.03; 95% CI, 1.02-1.04; $P < 0.001$), baseline immunosuppression (HR for CNI+mycophenolic acid versus others, 0.74; 95% CI, 0.57-0.96; $P = 0.02$), time since transplantation (HR for each month, 1.003; 95% CI, 1.002-1.005; $P < 0.001$), platelet count at ICU admission (HR for every 1000 cells/mm$^3$, 0.998; 95% CI, 0.996-0.999; $P < 0.001$), and sepsis as the reason for ICU admission (HR, 1.67; 95% CI, 1.28-2.20; $P < 0.001$).

## DISCUSSION

Implementing multifaceted control intervention actions significantly reduces the incidence of HAIs. The effect of

**TABLE 1.**

**Baseline characteristics, variables at ICU admission, events, and rates of devices usage, stratified by pre- and postimplementation eras**

| Variable | Total (N = 798) | Pre (n = 449) | Post (n = 349) | *P* |
|---|---|---|---|---|
| Baseline characteristics | | | | |
| Age, y | 58.0 (47.0-65.0) | 57.0 (48.0-65.0) | 58.0 (47.1-66.1) | 0.31 |
| Male, n (%) | 473 (59.3) | 266 (59.2) | 207 (59.3) | 0.98 |
| White, n (%) | 498 (62.4) | 276 (61.5) | 22 (63.6) | 0.86 |
| Cause of CKD, n (%) | | | | 0.77 |
| Hypertension | 273 (34.2) | 158 (35.2) | 115 (33.0) | |
| Diabetes | 206 (25.8) | 121 (26.9) | 85 (24.4) | |
| Glomerulopathies | 83 (10.4) | 44 (9.8) | 30 (11.2) | |
| Others | 236 (29.6) | 126 (28.1) | 110 (31.5) | |
| Deceased donor, n (%) | 616 (77.2) | 362 (80.6) | 254 (72.8) | 0.009 |
| Posttransplant diabetes[a] | 150 (18.9) | 81 (18.2) | 69 (19.2) | 0.59 |
| Charlson Comorbidity Index, n | 5.0 (4.0-7.0) | 5.0 (4.0-7.0) | 5.0 (4.0-7.0) | 0.89 |
| Immunosuppression, n (%) | | | | 0.07 |
| CNI+MPA | 372 (46.6) | 221 (49.2) | 151 (43.3) | |
| CNI+AZA | 207 (25.9) | 102 (22.7) | 105 (30.1) | |
| CNI+mTORi | 61 (7.6) | 39 (8.7) | 22 (6.3) | |
| Others | 159 (19.9) | 87 (19.7) | 72 (20.6) | |
| ICU admission | | | | |
| Time since transplantation, mo | 58.9 (5.3-114.5) | 47.0 (1.7-110.8) | 65.2 (21.1-119.8) | 0.001 |
| Reason for admission, n (%) | | | | 0.56 |
| Sepsis | 201 (25.2) | 115 (25.6) | 86 (24.8) | |
| Nontransplant surgery | 159 (19.9) | 97 (21.6) | 62 (17.8) | |
| Acute respiratory failure | 134 (16.8) | 67 (14.9) | 67 (19.2) | |
| Neurologic disorder | 100 (12.5) | 53 (11.8) | 47 (13.5) | |
| Cardiovascular | 64 (8.0) | 39 (8.7) | 25 (7.2) | |
| Bleeding | 36 (4.5) | 19 (4.2) | 17 (4.9) | |
| Others | 104 (13.0) | 59 (13.1) | 45 (12.9) | |
| SOFA, n | 6.0 (4.0-9.0) | 6.0 (4.0-9.5) | 5.0 (3.0-8.0) | 0.001 |
| SAPS III, n | 52.0 (44.0-60.0) | 53.0 (44.0-61.0) | 51.0 (44.0-59.0) | 0.22 |
| eGFR,[a] mL/min/1.73 $m^2$ | 20.0 (10.5-36.3) | 20.4 (9.4-32.5) | 19.8 (12.4-40.9) | 0.02 |
| Hemoglobin, g/dL | 9.8 (8.4-11.4) | 9.8 (8.4-11.4) | 9.7 (8.3-11.4) | 0.99 |
| Platelets, 1000 cells/$mm^3$ | 155 (106-210) | 151 (104-205) | 156 (112-219) | 0.23 |
| Events after ICU admission, n (%) | | | | |
| Use of vasopressor | 397 (49.7) | 225 (50.1) | 172 (49.3) | 0.82 |
| AKI | 617 (77.3) | 359 (80.0) | 258 (73.9) | 0.04 |
| RRT | 392 (49.1) | 225 (50.1) | 167 (47.9) | 0.53 |
| Rates of devices usage, n (%) | | | | |
| CVC | 657 (82.3) | 353 (78.6) | 304 (87.1) | 0.002 |
| UC | 564 (70.7) | 323 (71.9) | 241 (69.1) | 0.37 |
| MV | 362 (45.4) | 196 (43.7) | 166 (47.6) | 0.27 |
| Rates of d-HAIs, n (%) | | | | |
| d-HAIs | 53 (6.6) | 39 (8.7) | 14 (4.0) | 0.009 |
| CLABSI | 42 (6.4) | 30 (8.5) | 12 (3.9) | 0.017 |
| CAUTI | 6 (1.05) | 5 (1.5) | 1 (0.4) | 0.34 |
| VAP | 5 (1.38) | 4 (2.0) | 1 (0.6) | 0.38 |
| Rates of death, n (%) | | | | |
| 30 d | 198 (24.8) | 102 (22.7) | 96 (27.5) | 0.12 |
| 90 d | 244 (30.6) | 124 (27.6) | 120 (34.4) | 0.04 |

[a]Missing: posttransplant diabetes, n = 5; eGFR, n = 2.

AKI, acute kidney injury; AZA, azathioprine; CAUTI, catheter-associated urinary tract infection; CLABSI, central line-associated bloodstream infection; CNI, calcineurin inhibitor; CKD chronic kidney disease; CVC, central venous catheter; d-HAI, device-related healthcare-associated infection; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; MPA, mycophenolic acid; MPS, mycophenolate sodium; mTORi, mammalian target of receptors inhibitor; MV, mechanical ventilation; RRT, renal replacement therapy; SAPS III, Simplified Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment; UC, urinary catheter; VAP, ventilator-associated pneumonia.

these strategies was recently measured in a meta-analysis of 144 studies evaluating the impact on various types of HAIs and demonstrating a risk reduction of 54% for CLABSI, 46% for CAUTI, and 38% for VAP.[10] These reductions are similar across different socioeconomic development strata of the countries. Notably, the studies stratified their analyses by the types of HAIs, with a particular focus on those related to devices,[25] and there are also published studies in specific

**TABLE 2.**

**Multivariable analysis for device-related HAIs**

| Variables | RR | 95% CI | *P* |
|---|---|---|---|
| Reason for ICU admission (sepsis vs others) | 0.83 | 0.44-1.58 | 0.574 |
| Charlson Comorbidity Index (for each point) | 1.04 | 0.95-1.13 | 0.376 |
| Time after transplantation (for each month) | 1.00 | 1.00-1.00 | 0.199 |
| Hemoglobin* (for each 1 g/dL) | 0.89 | 0.80-0.99 | 0.032 |
| Platelets* (for every 1000 cells/mm$^3$) | 0.996 | 0.993-1.000 | 0.031 |
| eGFR* (for each 1 mL/min) | 1.01 | 1.002-1.020 | 0.021 |
| Era (post- vs preimplementation) | 0.42 | 0.23-0.77 | 0.005 |

CI, confidence interval; eGFR, estimated glomerular filtration rate; HAI, healthcare-associated infection; ICU, intensive care unit; RR, relative risk.*At ICU admission.

high-risk populations, such as hemodialysis patients,[26] but not among KTRs. To our knowledge, this cohort is the first to measure such an impact in this population, demonstrating a 60% reduction in the risk for HAIs with the implementation of bundles. However, despite this reduction, the occurrence of d-HAIs even in the post–bundle implementation period substantially increased the risk of mortality in these patients.

The impact of HAIs on patient outcomes is unequivocal and has been one of the primary catalysts for initiatives to implement reduction and control measures.[27] Among the widely impacted outcomes, notable are the increased length of hospitalization, readmission rates, and disabilities resulting in an inability to work, all of which lead to heightened hospital and social costs and, clearly, an increased risk of mortality.[28,29] In addition to the global impact, specific types of HAIs present distinct risks, with a higher incidence of death attributed to CLABSI, ranging from 10% to 40%, followed by VAP, from 7% to 34%.[30] Our study measured the impact of d-HAIs on mortality risk, specifically in KTRs admitted to specialized ICUs. We observed this impact using 2 measurement strategies: survival analysis and calculating the RR of mortality based on the presence of d-HAIs.

The impact of d-HAIs on the mortality risk was evident in all the analyses conducted, regardless of the implementation of prevention bundles. Patients who developed d-HAIs had a 30% lower survival rate 90 d after ICU admission, and the occurrence of d-HAIs, irrespective of the study period, increased the risk of mortality by 2.6 times. Notably, the RR of mortality attributed to d-HAIs was similar in both eras. A recent study conducted in a middle-income country evaluated the impact of HAIs on >32 000 patients admitted to ICUs across 547 hospitals, finding a mortality incidence of 40% in patients with HAIs.[31] Focusing on patients with CKD on dialysis, a study in 2019 that included patients from 2 public hospitals in Malaysia observed a reduction in life expectancy from 22.7 to 19.9 mo when these patients developed HAIs.[32] The straightforward survival analysis based on such a severe event as HAIs in an ICU population can present some drawbacks, such as confounding factors, notably age, reason for admission, and severity, among others. The multivariable analysis used in our study can mitigate these interferences, and indeed, we observed that d-HAIs resulted in a substantial increase in the risk of death, regardless of patient age, the reason for admission, severity markers, transplant duration (a specific variable in our population), and the study period.

In our cohort, patients were admitted to the ICU for various reasons and with moderate severity indices, as demonstrated by the SOFA and SAPS III scores. Additionally, most patients require advanced life care, such as vasopressor, MV, or RRT,

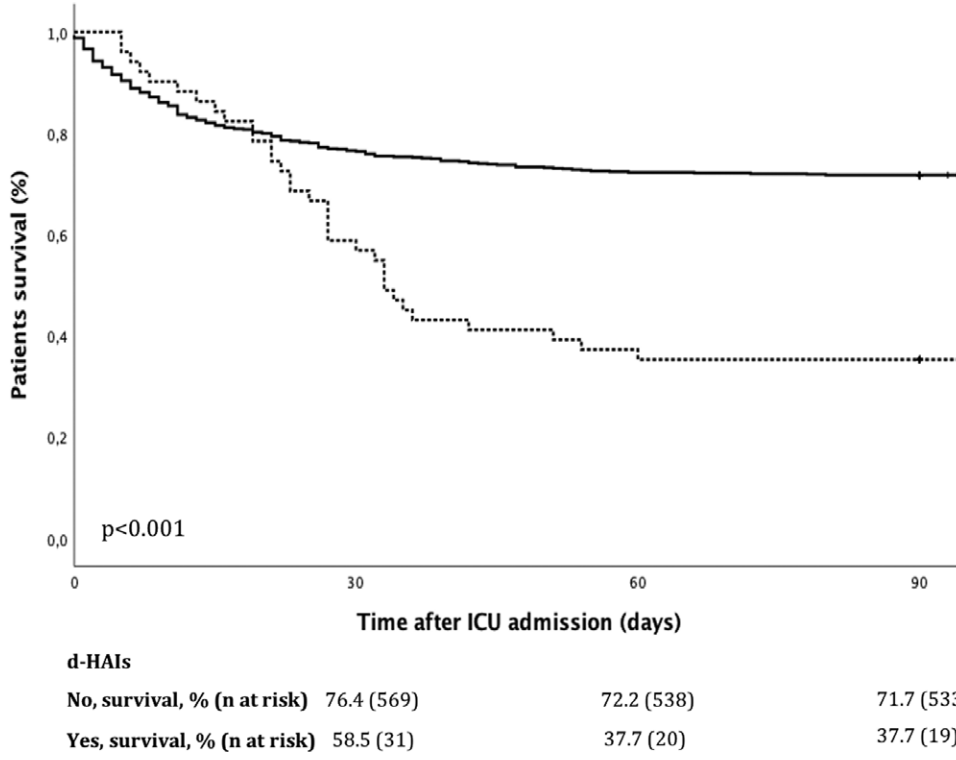


**FIGURE 2.** Patient survival after ICU admission stratified by d-HAIs. The solid line represents the survival curve of patients who did not have d-HAIs, whereas the dotted line represents the survival curve of those who did. d-HAI, device-related healthcare-associated infection; ICU, intensive care unit.

**TABLE 3.**

**Multivariable analysis for death**

| Variable | HR | 95%CI | *P* |
|---|---|---|---|
| Immunosuppression (CNI+MPS vs other) | 0.74 | 0.57-0.96 | 0.024 |
| Age (for each year old) | 1.03 | 1.02-1.04 | <0.001 |
| Time after transplantation (for each month) | 1.003 | 1.002-1.005 | <0.001 |
| Platelets* (for every 1000 cells/mm$^3$) | 0.998 | 0.996-0.999 | <0.001 |
| Reason for ICU admission (sepsis vs others) | 1.67 | 1.28-2.20 | <0.001 |
| d-HAIs | 2.63 | 1.80-3.84 | <0.001 |

CI, confidence interval; CNI, calcineurin inhibitor; d-HAI, device-related healthcare-associated infection; HR, hazard ratio; ICU, intensive care unit; MPS, mycophenolate sodium.

which, per se, constitutes a high risk of mortality. Thus, it is crucial to acknowledge that patients were already at a high risk of death before being exposed to the risk of developing one of the HAIs. Therefore, for the multivariable model for the risk of mortality and the occurrence of HAIs, we considered only those variables present in all patients at the time of admission. Because not all patients had sufficient exposure time for the occurrence of HAIs, either due to early death or ICU discharge, we assessed the effect of patient characteristics on the risk of death through Poisson regression, considering the exposure time.[33]

Thus, the HAI variable was treated as a predictor and dependent variable, with risk estimates measured through generalized structural equations. We found that regardless of other predictor factors and considering the competition between the risk of death and the occurrence of HAIs, the latter increased the likelihood of the patient dying within 90 d of ICU admission by >2.6 times. This finding was independent of the eras in which the HAIs and deaths occurred. These findings demonstrate that even with the implementation of control bundles, there remains a need to manage the residual risk, justifying all currently adopted policies calling for zero tolerance.[34,35]

Accounting for the 3 types of d-HAIs, we observed that implementing bundles reduced the incidence of cases in line with findings from various studies.[10,25] However, a simple comparison of event frequencies between the 2 eras may not accurately reflect the extent of this reduction, as patients in the 2 eras exhibited different characteristics that could influence the likelihood of HAIs. To better assess the magnitude of the impact of bundle implementation, we opted to estimate its impact through risk estimates using a Poisson model. We observed a 58% reduction in the probability of d-HAI occurrence, independent of other variables. In a study conducted in a general adult ICU in the same city as our center, this effect notably persisted over time in nonstratified populations when the observation was extended for a period of 22 y: from 1996 to 2006, the era before the implementation of measures, and from 2007 to 2017, the postimplementation era, showing declines of 58.6% in CLABSI, 56.7% in CAUTIs, and 82.6% in VAP.[36]

Although our study is the first real-life investigation into the impact of multifaceted control interventions on the incidence of HAIs and the associated risk of death among KTRs, it has some limitations that must be highlighted. First, we must consider the limitations imposed by the nature of the study itself. Although it is a natural experiment, underscoring relevant results from real life, it remains an observational and historical study, subject to selection bias, information loss, and classification error. As previously noted, some differences were observed in certain variables when patients were stratified according to the 2 study eras, before and after the implementation of bundles. This could be mitigated by using matching strategies and controlling for variables. Although these strategies are more appropriate for balancing potential differences, they may need to be more feasible in studies of low-frequency events. Additionally, it is important to consider that this study was conducted at a single center with a high volume of transplants and a highly specialized team, including an ICU dedicated to caring for such patients, with low turnover in the multidisciplinary team. Therefore, these results could only be partially reproducible in other centers.

In conclusion, in our study, we demonstrated the impact of d-HAIs on survival chances among KTRs admitted to the ICU due to acute illness requiring critical care. Consistent with the best evidence, we also showed that implementing multifaceted control intervention actions in an ICU specialized in kidney transplant care significantly reduced the incidence of d-HAIs, with a similar magnitude observed even without stratifying for clinical vulnerability. However, despite these measures, the persistent risk of death when each d-HAI occurred underscored the need for a zero-tolerance policy toward these infections.

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