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## Risk factors for health care–associated infection in hospitalized adults: Systematic review and meta-analysis



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## Key Words:

Risk factors  
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**Background:** Health care–associated infections (HAIs) are a public health problem that increase health care costs. This article aimed to systematically review the literature and meta-analyze studies investigating risk factors (RFs) independently associated with HAIs in hospitalized adults.

**Methods:** Electronic databases (MEDLINE, Embase, and LILACS) were searched to identify studies from 2009–2016. Pooled risk ratios (RRs) or odds ratios (ORs) or mean differences (MDs) and 95% confidence intervals (CIs) were calculated and compared across the groups. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

**Results:** Of 867 studies, 65 met the criteria for review, and the data of 18 were summarized in the meta-analysis. The major RFs independently associated with HAIs were diabetes mellitus (RR, 1.76; 95% CI, 1.27–2.44), immunosuppression (RR, 1.24; 95% CI, 1.04–1.47), body temperature (MD, 0.62; 95% CI, 0.41–0.83), surgery time in minutes (MD, 34.53; 95% CI, 22.17–46.89), reoperation (RR, 7.94; 95% CI, 5.49–11.48), cephalosporin exposure (RR, 1.77; 95% CI, 1.30–2.42), days of exposure to central venous catheter (MD, 5.20; 95% CI, 4.91–5.48), intensive care unit (ICU) admission (RR, 3.76; 95% CI, 1.79–7.92), ICU stay in days (MD, 21.30; 95% CI, 19.81–22.79), and mechanical ventilation (OR, 12.95; 95% CI, 6.28–26.73).

**Conclusions:** Identifying RFs that contribute to develop HAIs may support the implementation of strategies for their prevention, therefore maximizing patient safety.

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Health care–associated infections (HAIs) have become a global public health problem that involves serious health risks and increases health care costs each year. Human suffering is an immediate implication of these infections, given that they reduce the quality of life of patients and their relatives.<sup>1,2</sup>

A U.S. prevalence survey estimated that there were 722,000 HAIs in hospitals and approximately 75,000 HAI-related deaths in 2011, with >50% occurring outside intensive care units (ICUs).<sup>1</sup> Each year in Europe, HAIs cause 16 million additional hospitalization days, cause 37,000 attributable deaths, and contribute to an additional

110,000 deaths. Annual financial losses are estimated at around €7 billion, including direct costs. Information about epidemiology of HAIs in low- and middle-income countries is very scarce, with limited published data available.<sup>3</sup>

Any infection that a patient contracts after hospitalization is considered an HAI, regardless of procedure or department, including outpatient and homecare treatment, and infections acquired from health professionals.<sup>4</sup> Several risk factors (RFs) predispose patients to develop HAIs. Intrinsic RFs encompass the physiologic characteristics or conditions of the individual at the time of admission, and extrinsic RFs involve all measures related to the treatment instituted to the patient.<sup>5</sup>

In the hospital context, there are a number of RFs associated with HAIs; however, there must be an adequate number of pathogens present to cause an infection. Infectious agents transmitted during health care are primarily derived from human sources, but inanimate environmental sources have also been implicated in transmission.<sup>6</sup> Among the RFs for HAIs are health and disease status,

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treatment, invasiveness, and environmental methods to which the patient are exposed. Therefore, the determinants of hospital infection risk are the characteristics and exposures of patients that predispose them to infections. The epidemiology of HAIs shows that some RFs are nonmodifiable.<sup>7</sup>

According to the European Centre for Disease Prevention and Control, approximately 20%–30% of HAIs are considered preventable through intensive hygiene and control programs.<sup>8</sup> Most prevention measures are costly; however, in many cases, they are well below the cost of treating patients with HAIs. Prevention efforts must begin with a culture change in patient care because it is known that controlling and preventing hospital infections represent a challenge for patient safety and quality of care. However, for these changes to occur, it is necessary to understand which factors increase a patient's risk of acquiring an infection.

It is essential, therefore, to determine the RFs that contribute to HAIs. Most related studies have focused only on a single RF, but given the complexity and extent of the subject, there is a need for broad global investigation into which factors are frequently presented by patients and the relationships these factors have with HAIs, because the implementation of procedures, interventions, and measures to eliminate or minimize HAIs depends on their adequate recognition in different hospital environments. Therefore, this study aimed to systematically review the literature and meta-analyze studies investigating RFs independently associated with HAIs in hospitalized adults.

## METHODS

This systematic review (SR) and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.<sup>9</sup> The protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews (registration no. CRD42016042487).

### Data sources and search strategy

The following 3 databases made available by the Federal University of Rio Grande do Sul were used: PubMed/MEDLINE, Embase, and LILACS. The 3 databases cited were chosen for their representativeness in the health area and for having a wide range of scientific production in North America, Europe, Latin America, and the Caribbean.

The electronic search was performed on databases including publications from January 2009–December 2016 using Descriptors in Health Sciences in Brazilian Virtual Health Library for searches in LILACS, Medical Subject Headings terms for searches in PubMed/MEDLINE, and Embase Subject Headings terms for searches in Embase according to the strategies subsequently described.

The following search strategies were used: PubMed/MEDLINE: risk assessment[majr] OR inpatients[majr] OR patient safety[majr] OR risk factors[majr] OR infection control[majr] OR cross infection[majr] AND risk factors AND infection; Embase: "risk assessment"/exp/mj OR "inpatients"/exp/mj OR "patient safety"/exp/mj OR "infection"/exp/mj OR "infection control"/exp/mj OR "cross infection"/exp AND "risk factors"; and LILACS: (tw:(risk assessment)) OR (tw:(inpatients)) OR (tw:(patient safety)) OR (tw:(infection control)) OR (tw:(cross infection)) AND (tw:(risk factors)) AND (tw:(infection)).

### Study inclusion and exclusion criteria

We included analytical observational studies, randomized clinical trials (RCTs), and SRs published in Portuguese, English, or Spanish that addressed infection RFs in hospitalized adults or estimated RFs

independently associated with HAIs. Editorials letters, conference summaries, qualitative and descriptive studies, and articles addressing mortality-related RFs were excluded.

### Data extraction

Article identification and selection were conducted independently by 2 reviewers (A.L.R.-A. and B.E.). Disagreements were resolved by discussion with and analysis by a third reviewer (W.C.-M.). Articles identified in duplicate in several databases were computed only once. Zotero, version 4.0.28.7 (Center for History and New Media, George Mason University, Fairfax, VA) was used to store references and remove duplicates.

### Quality assessment

The methodologic quality of the included studies was evaluated using 3 instruments: the Newcastle-Ottawa Scale (NOS),<sup>10</sup> Assessment of Multiple Systematic Reviews (AMSTAR),<sup>11</sup> and the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. The Cochrane Collaboration risk of bias tool for RCTs is available in RevMan 5.1 (Cochrane Community, Copenhagen, Denmark). Joanna Briggs Institute (JBI) recommendations were used to evaluate the evidence level of the studies.

### Data analysis

RevMan 5.1 software was used for analysis. A meta-analysis was performed to compute the pooled effect estimate with a random-effects model for either binary or continuous outcomes when there were at least 2 studies included. For dichotomous outcomes, the Mantel-Haenszel method was applied to calculate the risk ratio (RR) or odds ratio (OR) and corresponding 95% confidence interval (CI). For continuous outcomes, the inverse variance weighting was applied to calculate the mean difference (MD) and corresponding 95% CI. Statistical heterogeneity was evaluated using the  $I^2$  statistic. The data abstracted from the individual studies were pooled to determine the effect estimate. Publication bias was assessed using a funnel plot.

## RESULTS

### Identification and selection of studies

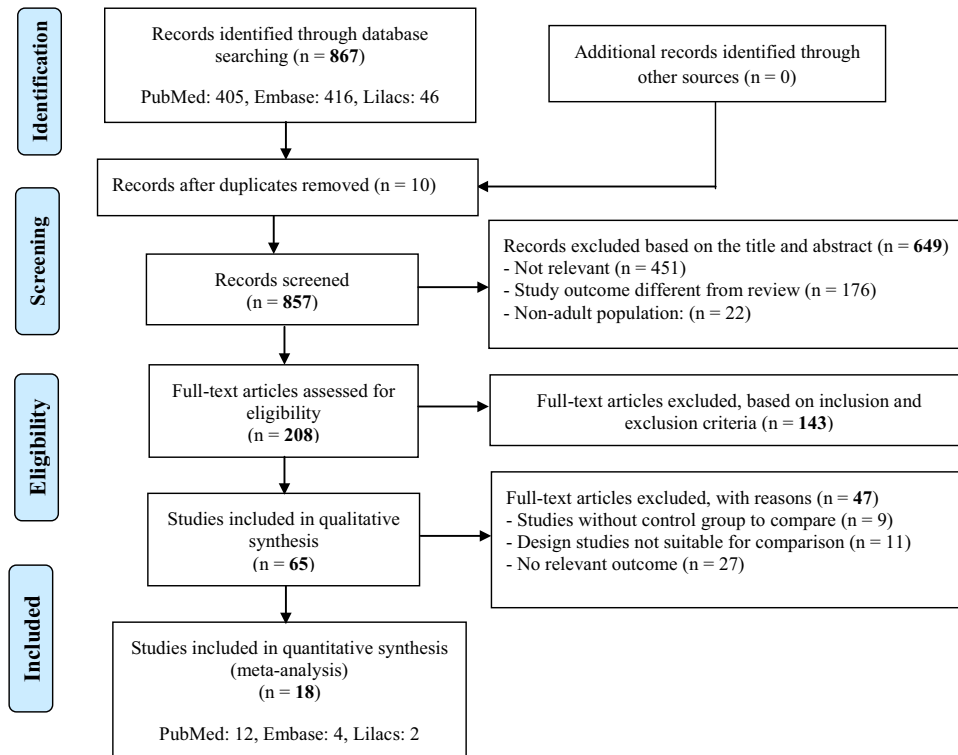
A total of 867 articles were identified, of which 65 studies were included in the SR, and the data of 18 were summarized in the meta-analysis. The flowchart for the selection and exclusion of studies is presented in [Figure 1](#).

### Characteristics of the included studies

An overview of the studies is provided in [Supplementary Table S1](#), showing a summary of the selected studies, including authors, year of publication, country, RFs for infection, design, and methodologic quality according to the NOS and AMSTAR tools, and the JBI evidence levels.

The distribution showed a recent downward trend: 38 (58.5%) of the studies were published between 2009 and 2012, whereas 27 (41.5%) were published between 2013 and 2016. Most of the studies had an observational design: there were 40 (61.5%) prospective-retrospective cohort studies, 14 (21.6%) were case-control studies, 5 (7.7%) were cross-sectional studies, 5 (7.7%) were SRs, and 1 (1.5%) was an RCT.

The studies were conducted in a total of 24 different countries: 10 (15.4%) in the United States; 7 (10.8%) in Spain; 5 (7.7%) each in Brazil, France, Turkey, and the United Kingdom; 3 (4.6%) each in



**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart summarizing the process for the identification of the eligible studies.

China and Italy; 2 (3.0%) each in Colombia, Germany, Korea, and The Netherlands; and 1 (1.5%) each in Belgium, Canada, Greece, Israel, Japan, Iran, Peru, Romania, Mexico, and Serbia. There were 4 (6.0%) multicenter studies.

#### Quality assessment of included studies

On careful evaluation, the NOS scores of 54 of the cohort and case-control studies were  $\geq 6$  stars. For cross-sectional studies, the minimum score was 4 stars and the maximum score was 5. Of the 5 SRs, 3 were categorized as low quality (AMSTAR score 0–4) and 2 were moderate quality (AMSTAR score 5–8), indicating structural and methodologic variability among the articles. The scoring is presented in [Supplementary Table S1](#). The JBI evidence-level classifications were distributed as follows: level 1, 2 studies; level 3, 62 studies; and level 4, 1 study.

#### Intrinsic RFs for infection

In this SR, 40 of the included studies were cohort studies, among which the most frequently observed RFs were age,<sup>12–19</sup> diabetes mellitus (DM),<sup>15,17–21</sup> chronic obstructive pulmonary disease<sup>13,15,19,22</sup> and type of diagnosis (gastrointestinal, cardiovascular or trauma),<sup>14–16,23</sup> body mass index,<sup>13,19,24</sup> compromised immune system,<sup>23,25,26</sup> male sex,<sup>20,22,27</sup> female sex,<sup>15,18</sup> weight loss,<sup>13,15</sup> smoking,<sup>13,15</sup> temperature  $\geq 38.5^\circ\text{C}$  or  $\leq 36.0^\circ\text{C}$ ,<sup>28,29</sup> medicated hypertension,<sup>15,26</sup> serum albumin levels ( $<3.0\text{ g/dL}$ ),<sup>12,30</sup> and anemia.<sup>16,24</sup> In contrast, several studies observed a lower proportion of other intrinsic RFs ([Supplementary Table S1](#)).<sup>31,32</sup>

There were fewer intrinsic RFs found in the 12 case-control studies: age,<sup>33</sup> male sex,<sup>34</sup> nervous system diseases,<sup>33</sup> chronic renal failure,<sup>35</sup> acute respiratory distress syndrome,<sup>36</sup> chronic obstructive pulmonary disease,<sup>37,38</sup> previous episode of pneumonia,<sup>39</sup> DM,<sup>37</sup> urinary incontinence,<sup>34</sup> obesity,<sup>34</sup> nonsurgical wounds<sup>40</sup> and local-

ized head and neck burns,<sup>41</sup> serum albumin  $<3.0\text{ g/dL}$ ,<sup>39</sup> white blood cells count  $>12,000/\text{mm}^3$ .<sup>39</sup>

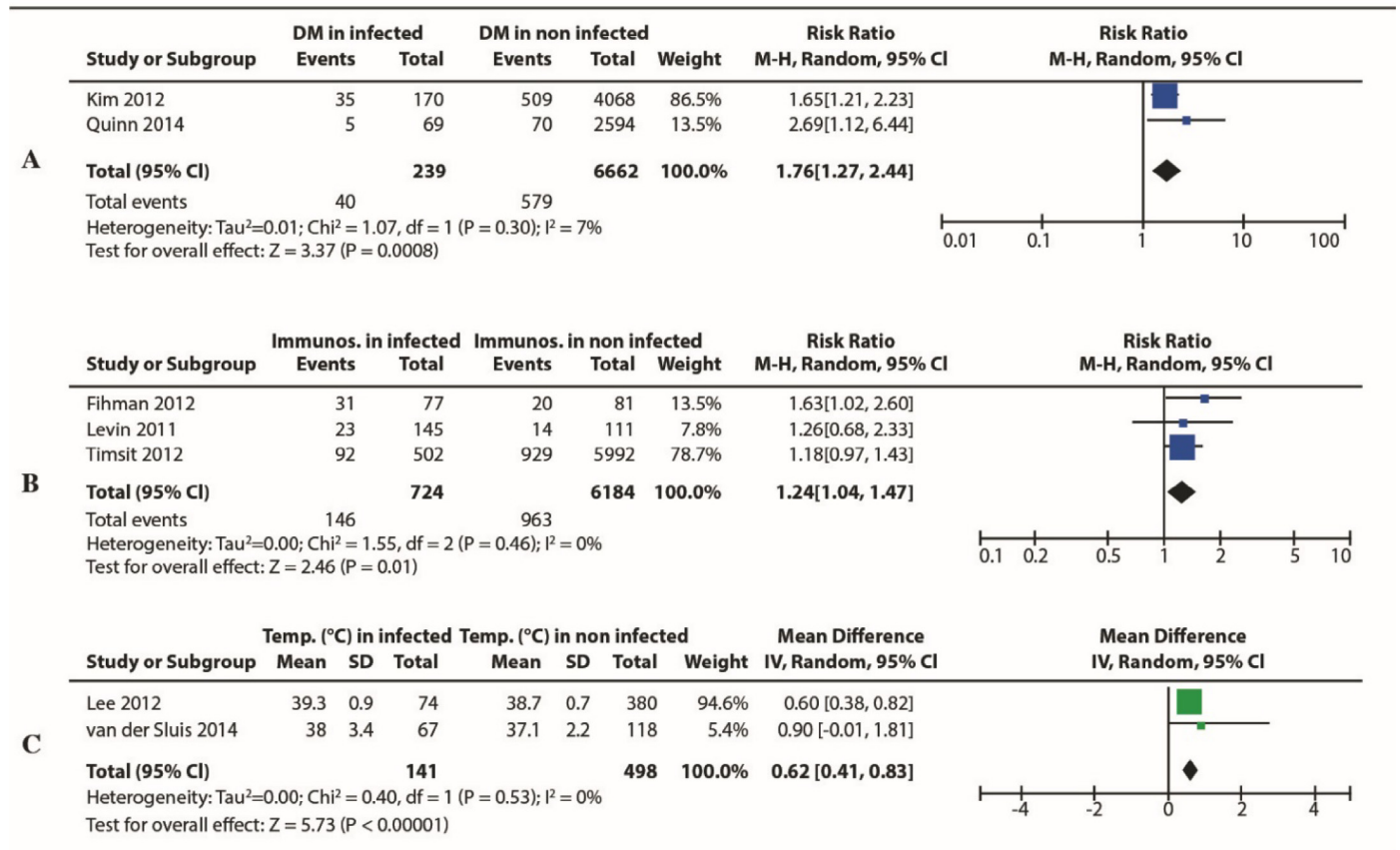
In the 5 included SRs, DM<sup>42–45</sup> was the most prevalent intrinsic RF, followed by acute renal failure<sup>43,45</sup> and potential renal failure currently on dialysis.<sup>42</sup> Other factors were found in lower percentages ([Supplementary Table S1](#)).

Intrinsic RFs observed in the cross-sectional studies were distributed more homogeneously: age  $>65$  years,<sup>46,47</sup> male sex,<sup>47</sup> terminal incurable disease,<sup>48</sup> hematology,<sup>48</sup> gastrointestinal diseases,<sup>49</sup> and the presence of  $>2$  underlying diseases.<sup>49</sup> No intrinsic RF for infection was found in the RCT.

#### Extrinsic RFs for infection

In the cohort studies, the observed extrinsic RFs were central venous catheter (CVC) placement,<sup>23,25,50–53</sup> ICU admission,<sup>54–58</sup> duration of surgery,<sup>13,17,20,24</sup> steroid use,<sup>13,15,59</sup> previous antibiotic use,<sup>55,60</sup> exposure to cephalosporins before the first episode of infection,<sup>58,61</sup> number of administered antibiotics,<sup>53,62</sup> antimicrobial therapy within 90 days,<sup>63</sup> reoperation,<sup>20,64</sup> transfusion,<sup>50,56,64</sup> invasive mechanical ventilation (IMV),<sup>50,52,65</sup> hospitalization time,<sup>66,67</sup> and a high score on the Acute Physiology and Chronic Health Disease Classification System II.<sup>14,55</sup> Other less frequent extrinsic RFs were found ([Supplementary Table S1](#)).<sup>65,68</sup>

It was observed that in the case-control studies, the most prevalent extrinsic RF was IMV,<sup>40,69,70</sup> followed by previous hospitalization,<sup>35,39</sup> hospitalization time,<sup>71</sup> low McCabe score at admission,<sup>34</sup> gastrostomy or central line-associated bloodstream infection at admission,<sup>34</sup> recent surgery,<sup>34</sup> acute graft rejection,<sup>38</sup> urologic surgery,<sup>35</sup> antacid use,<sup>33</sup> recent exposure to piperacillin-tazobactam,<sup>72</sup> antibiotic use within the last 3 months,<sup>35</sup> prolonged steroid use,<sup>36,39</sup> orotracheal intubation,<sup>70</sup> catheter use  $\geq 7$  days,<sup>73</sup> aspiration of secretions,<sup>70</sup> and high Abbreviated Burn Severity Index score.<sup>41</sup>



**Fig 2.** Forest plots of the intrinsic risk factors for infection in hospitalized adults: (A) diabetes mellitus, (B) immunosuppression, and (C) temperature (°C). CI, confidence interval; DM, diabetes mellitus; *Immunos.*, immunosuppression; *M-H*, Mantel-Haenszel; *Temp.*, temperature.

In the SRs, the most commonly mentioned extrinsic RFs were corticosteroid use,<sup>42-44</sup> IMV,<sup>42,43,74</sup> blood transfusion,<sup>42,45,74</sup> elective surgery,<sup>43,45</sup> CVC,<sup>43,44</sup> total parenteral nutrition<sup>43,45</sup> and abdominal surgery,<sup>44,45</sup> among others.

Extrinsic RFs cited in the cross-sectional studies included: patient origin,<sup>46</sup> hospital >300 beds,<sup>46</sup> current surgery or surgery in the last 12 months,<sup>48,49</sup> treatment by surgical specialists,<sup>47</sup> urinary catheter,<sup>46,48</sup> CVC,<sup>46,48</sup> urinary catheterization  $\geq 7$  days,<sup>75</sup> intubation,<sup>75</sup> tracheostomy,<sup>75</sup> nasogastric tube,<sup>75</sup> application of specific medical techniques such as drainage, vascular, and catheters,<sup>49</sup> treatment with antibiotics in the last 6 months,<sup>49</sup> and combined antibiotic therapy.<sup>75</sup> In the RCT, insertion of the catheter into the jugular vein and duration of catheter >7 days were the observed extrinsic RFs.<sup>76</sup>

### Meta-analysis

Data of 18 observational studies (cohort and case-control studies) were included in the meta-analysis. Seven studies featured data summarizing outcomes related to intrinsic RFs independently associated with HAIs (Fig 2). The intrinsic RFs with statistically significant differences between infected and uninfected patients were DM (RR, 1.76; 95% CI, 1.27-2.44), immunosuppression (RR, 1.24; 95% CI, 1.04-1.47), and body temperature (MD, 0.62; 95% CI, 0.41-0.83).

The meta-analysis of extrinsic RFs independently associated with HAIs involved outcomes from 13 studies (Fig 3 and Fig 4). Figure 3 presents the RFs related to surgical procedures and antibiotic therapy: surgery time in minutes (MD, 34.53; 95% CI, 22.17-46.89), reoperation (RR, 7.94; 95% CI, 5.49-11.48), and cephalosporin exposure (RR, 1.77; 95% CI, 1.30-2.42).

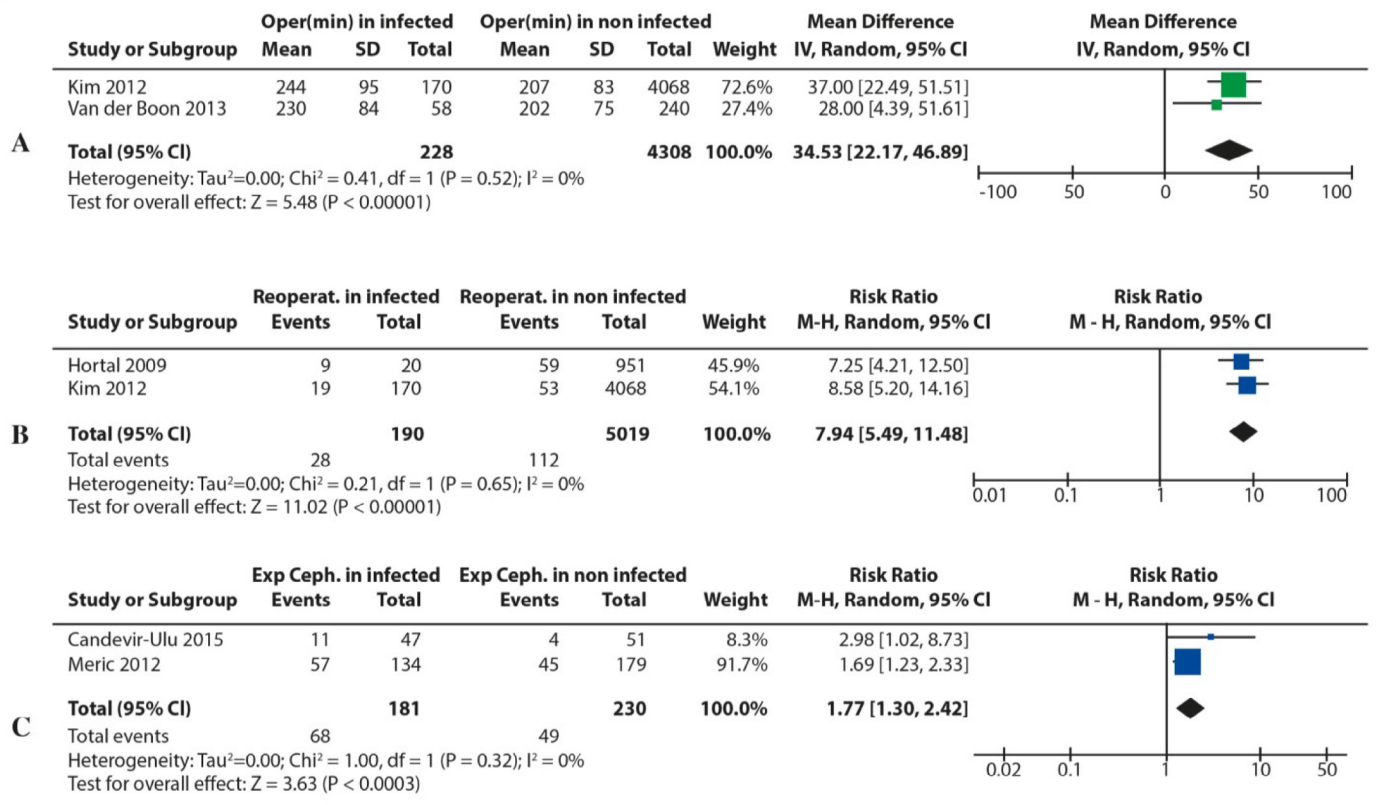
Figure 4 shows the summarized effects of RFs related to invasive procedures and admission or stay in ICU. The number of days of CVC exposure was higher in infected patients than in noninfected patients (MD, 5.20; 95% CI, 4.91-5.48). There was a higher HAIs prevalence in patients who had been admitted to the ICU (RR, 3.76; 95% CI, 1.79-7.92) and in those who remained more days in the ICU (MD, 21.30; 95% CI, 19.81-22.79). In the 3 case-control studies, there was a statistically significant effect with low heterogeneity ( $I^2 = 20\%$ ) for mechanical ventilation between cases and controls (OR, 12.95; 95% CI, 6.28-26.73).

### DISCUSSION

This SR with meta-analysis helps synthesize and update the evidence available in the literature about independently associated RFs for developing an HAI in hospitalized adults. This is a particularly important topic because the risks of acquiring an infection in the hospital are associated with increased exposure to certain factors, resulting in the presence of HAIs. In this study, analyses of the RFs were performed separately because of differences in the nature of the factors.

#### Intrinsic RFs for infection

DM was identified in 2 studies<sup>20,21</sup> that have demonstrated statistically significant differences. An Italian epidemiologic surveillance program in 18 ICUs with a total sample of 5,561 patients concluded that DM is associated with twice the risk of developing an abdominal surgery-related infection and 4 times the risk of HAIs



**Fig 3.** Forest plots of the extrinsic risk factors for infection related to surgical procedures and antibiotic therapy in hospitalized adults: (A) operation time (minutes), (B) reoperation, and (C) exposure to cephalosporins. *CI*, confidence interval; *Ceph.*, cephalosporins; *Exp.*, exposure; *M-H*, Mantel-Haenszel; *(min)*, minutes; *Oper.*, operation; *Reoperat.*, reoperation.

in the bloodstream.<sup>77</sup> The control of HAIs in DM patients therefore requires a multidisciplinary effort, with interventions to educate patients about maintaining glycemic control, especially those whose hyperglycemia is only discovered preoperatively.<sup>42</sup>

Immunosuppression was also found to be a major RFs in patients who developed HAIs.<sup>23,25,26</sup> A previous retrospective study of 290 patients undergoing a total of 669 sacral nerve modulation procedures concluded that immunosuppression was an independent RF for infection.<sup>78</sup>

However, with health care being increasingly delivered in settings other than the traditional inpatient hospital wards, a bigger effort will need to be set forth to prevent or rapidly diagnose HAIs.<sup>79</sup> Although the epidemiology of infection among immunocompromised patients has been intensely studied for decades, there is little evidence to support the claim that all infections should be considered HAIs among immunocompromised patients.<sup>80</sup>

Included studies also reported that the body temperature of infected patients was higher than that of noninfected patients<sup>28,29</sup>; however, this factor requires further investigation in clinical settings. Lack of knowledge about this subject could delay the diagnosis of serious heat-sensitive diseases, compromising treatment and endangering lives.<sup>81</sup>

#### Extrinsic RFs for infection

Two studies reported surgery duration as a RF independently associated with HAIs.<sup>20,24</sup> In that context, a prospective study of 1,138 patients showed that a surgery >120 minutes was a RF for surgical site infection (OR, 4.3; 95% CI, 1.78–10.38).<sup>82</sup>

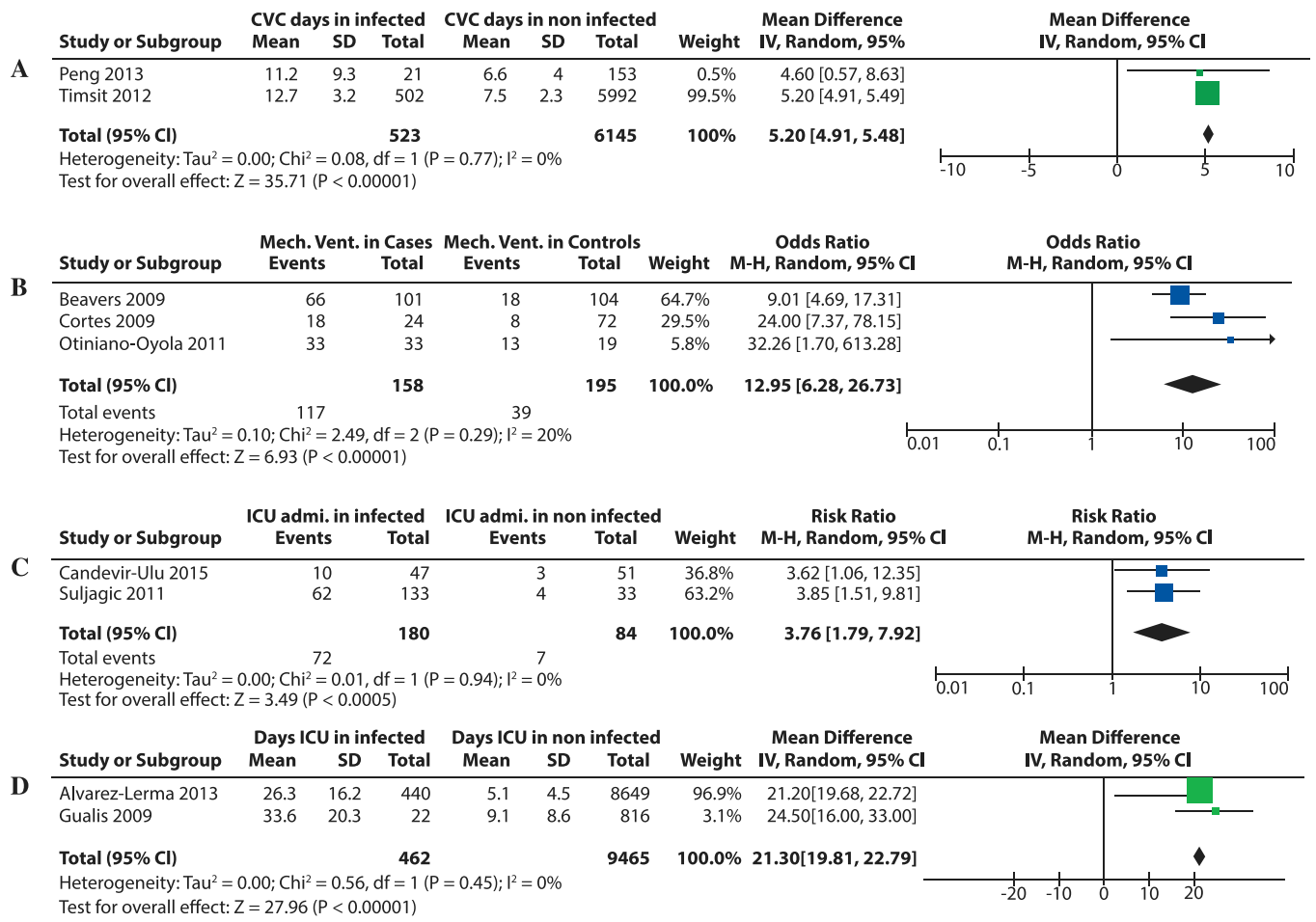
These data are similar to the results of another retrospective cohort study involving 4,588 lumbar fusion patients, in which increased surgery duration was associated with a progressive increase in the risk of global complications (OR, 2.1–5.7), medical complications (OR, 2.2–6.2), surgical complications (OR, 1.7–2.9), superficial surgical site infection (OR, 2.7–4.0), and postoperative transfusions (OR, 3.3–12.2).<sup>83</sup> Therefore, to improve patient outcomes, it is necessary to develop strategies for preventing surgical site infection that focus on surgical duration.<sup>82</sup>

Two studies<sup>20,64</sup> found a significant association between reoperation and HAI. According to another study, unplanned reoperation was a RF associated with operative wound infection (OR, 3.86; 95% CI, 2.85–5.24).<sup>84</sup>

With respect to the prior use of antibiotics, exposure to cephalosporins was also observed as a RF for HAI.<sup>58,61</sup> One study evaluating this RF revealed that the use of antimicrobials in the 10 days prior to diagnosis of hospital-acquired pneumonia was the only independent predictive factor of infection by multiresistant strains (OR, 3.45; 95% CI, 1.56–7.61).<sup>60</sup>

Our findings are in consonance with the results of a recent study showing that prior use of antibiotics is the main factor for the presence of infectious health care-associated endocarditis.<sup>85</sup> It can therefore be inferred that the current state of antibiotic therapy has reached a critical point because indiscriminate usage is leading to both compromised immunity and increased resistance.

Another type of RF for HAI was days of exposure to CVC, which was observed in 2 studies.<sup>23,53</sup> Several conditions have been reported in the literature as RFs for CVC-related infections, including failure to disinfect infusion systems,<sup>86</sup> frequent catheter handling and using the catheter to measure central venous pressure,



**Fig 4.** Forest plots of the extrinsic risk factors for infection in hospitalized adults related to invasive procedures and admission or stay in intensive care unit: (A) central venous catheter (days), (B) mechanical ventilation, (C) intensive care unit admission, and (D) intensive care unit stay time (days). *admi.*, admission; *CI*, confidence interval; *CVC*, central venous catheter; *ICU*, intensive care unit; *Mech.*, mechanical; *M-H*, Mantel-Haenszel; *Vent.*, ventilation.

dressings type, underlying disease, and clinical severity.<sup>87</sup> Catheter-related bloodstream infections are an important cause of morbidity and mortality in hospitalized patients. Of note, a recent network meta-analysis showed that in ICU patients, internal jugular and subclavian may, similarly, decrease catheter-related bloodstream infection risk, when compared with femoral.<sup>88</sup>

Mechanical ventilation was a significant RF for HAI in 3 case-control studies.<sup>40,69,70</sup> Although mechanical ventilation leads to improved oxygen exchange in the lungs, there are certain risks that predispose to the presence of HAI, such as prolonged intubation, reintubation, enteral feeding, aspiration, use of paralytic agents, extremes of age, severity of underlying pathophysiology, prior surgery, and prior antibiotic use.<sup>89-92</sup>

ICU admission<sup>56,58</sup> and days of ICU hospitalization<sup>55,57</sup> were other RFs for HAI. Other studies have also associated increased risk with the ICU, an environment that favors the natural selection of microorganisms because of the clinical severity of patients and the invasive procedures.<sup>93,94</sup>

*Limitations and future directions*

This study has developed a comprehensive review to identify the main RF for HAI in hospitalized adults. However, our study also has limitations. First, we only included published studies from 3

databases. Therefore, relevant articles published in other databases might have been missed. Second, it was only possible to perform meta-analysis with observational studies, which are inherently susceptible to bias and confounding. Third, publication bias could not be assessed because there were too few included studies to obtain summary estimates.

Finally, it is important to keep the topic of HAIs updated on a more global basis because the dynamics of integral assistance, technology, and the vulnerability of the individual are constantly changing. In hospital environments, it is possible to find a team committed to the prevention of HAIs; however, with limitations in the identification of RFs, often caused by lack of updating and continuing education, problems are triggered in the implementation of care, resulting in an increase of HAIs. Of note, despite the existence of recommendations for prevention of HAIs from international institutions, the constant monitoring of health practices, and the quality of care for patient safety in the control of HAIs, there is still a gap between theory and practice.<sup>7</sup>

**CONCLUSIONS**

This SR and meta-analysis identified extrinsic and intrinsic RFs that contribute to HAIs in hospitalized adults, which may facilitate the planning and implementation of strategies for their

prevention, control, and monitoring, therefore minimizing their occurrence and maximizing patient safety. Although significant progress has been made toward implementing good practice for infection prevention, further effort should be made to reduce the frequency of HAIs. It is also important that hospital managers familiarize themselves with the characteristics of HAIs and encourage health professionals to implement preventive measures. Nevertheless, it can be inferred that when health care units and their teams are familiar with the risks, they more easily adhere to prevention and control programs, contributing positively to control.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://dx.doi.org/10.1016/j.ajic.2017.08.016>.

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