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Review Article

# Mortality in patients with multidrug-resistant *Pseudomonas aeruginosa* infections: a meta-analysis

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## Abstract

*Pseudomonas aeruginosa* is the leading cause of nosocomial infections with high mortality rates owing to the limited therapeutic options for multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) and metallo-beta-lactamase (MBL)-producing strains. Herein, we present a meta-analysis exploring the association between MDRPA and São Paulo MBL-1 (SPM-1)-producing strains vs. mortality. Online databases were screened to identify studies published between 2006 and 2016. A total of 15 studies, comprising 3,201 cases of *P. aeruginosa* infection, were included. Our results demonstrated a higher mortality rate among patients infected with MDRPA (44.6%, 363/813) than those with non-MDRPA infection (24.8%, 593/2,388) [odds ratio (OR) 2.39, 95% confidence interval (CI) 1.70-3.36, $p$ <0.00001]. The risk of mortality in patients with non-SPM-1 strains was four times higher than that observed in the patients of the SPM-1 group; however, no statistically significant difference was observed ($p$ = 0.43). In conclusion, the results of our study demonstrated that patients infected with MDRPA had a significantly higher mortality rate than that of patients infected with non-MDRPA strains, especially patients with bloodstream infection (BSI), immunosuppression, and inadequate antimicrobial therapy. The absence of studies on the molecular aspects of *bla*SPM-1 and its association with mortality limited the analysis; therefore, our results should be interpreted with caution. Our findings also highlight the need for more studies on the molecular aspects of resistance and the peculiarities of different nosocomial settings.

**Keywords:** *Pseudomonas aeruginosa*. Mortality. Intensive care unit. Beta-lactamases. Nosocomial infection. Meta-analysis.

## INTRODUCTION

*Pseudomonas aeruginosa* is a versatile pathogen responsible for nosocomial infections with high mortality rates in critically ill patients, including those from general wards and outpatient clinics[1-4]. In recent decades, publications worldwide have highlighted the increasing issue of carbapenem and antipseudomonal broad-spectrum cephalosporin resistance[1,5,6]. The effect of bacterial resistance is directly related to infection severity and underlying disease, as well as the selected antibiotic therapy. Furthermore, the complexity of resistance mechanisms has contributed to a gradual increase in resistance rates, which are of particular concern in nosocomial settings[3,7,8].

Among the multiple resistance mechanisms in *P. aeruginosa,* including activation and overexpression of efflux systems and alteration of outer membrane permeability, the production of metallo-beta-lactamases (MBL), which can hydrolyze almost all beta-lactam agents, is one of the most important ones as it severely limits therapeutic options. Moreover, it also has been associated with prolonged hospitalization, polymicrobial infections, previous antibiotic use, and inadequate therapy[8-10].

So far, 10 major clinically important MBL groups have been identified, including Imipenemase-type metallo-ß-lactamase (IMP), Verona integron-encoded metallo-ß-lactamases, (VIM), São Paulo metallo-ß-lactamase (SPM), Germany imipenemase (GIM), Seoul imipenemase (SIM), New Delhi metallo-ß-lactamase (NDM), Kyorin Health Science metallo-ß-lactamase (KHM), Tripoli metallo-ß-lactamase (TMB), Dutch imipenemase (DIM) and Florence imipenemase (FIM). These MBL variants quickly spread across Europe, then to North America, Latin America, Asia, and Oceania, reflecting a problem of global dimensions[5,6,11,12]. A relevant aspect regarding this fast dissemination of resistance traits among *P. aeruginosa* strains is related to the fact that the resistance genotype may be transferred through mobile genetic elements. The emergence of multidrug-resistant (MDR) strains demonstrates the need for changes in routine laboratory diagnostic procedures, such as the incorporation of the molecular detection of *bla*-variant genes, particularly *bla*SPM-1, which is the most prevalent variant in Brazil[13-15].

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Several studies have reported conflicting results regarding mortality associated with multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) infections, and few reports have highlighted this association with MBL-producing strains[7,8,10,16,17]. Therefore, the present meta-analysis evaluated the association of MDR, the presence of the *bla*SPM-1 gene, and the risk of mortality in patients with *P. aeruginosa* infection.

## METHODS

### Search strategy and inclusion criteria

The studies were analyzed based on the essential standards listed in the 2011 C*ochrane Handbook for Systematic Review of Intervention*, edited by Higgin and Green[18]. A search of the PubMed, MEDLINE, BIREME, and Embase databases was conducted using the following keywords and combinations thereof: *Pseudomonas aeruginosa*, *P. aeruginosa*, multidrug-resistance, MDR, non-multidrug-resistance, non-MDR, *bla*SPM-1 gene, and mortality. The articles were examined by two investigators and studies published in English, Portuguese, and/or Spanish between 2006 and 2016 were included. Studies including (I) humans, (II) at least one group of comparison to MDRPA, and (III) mortality evaluation and antimicrobial resistance were included in the analysis. Unpublished articles (abstracts) or articles that did not fit these criteria were excluded from analysis.

### Data extraction and quality assessment

The data were extracted by two investigators. Information such as author, study period, study design, country, setting, definitions of mortality, mortality by MDRPA and non-MDRPA, and site of infection were extracted from each study, as well as whether the study authors had controlled for confounding clinical and demographic factors.

### Definition of MDR

Multidrug-resistant was defined as resistance to at least three different classes of antimicrobials, including carbapenems (imipenem, meropenem), antipseudomonal cephalosporins (ceftazidime and cefepime), fluoroquinolones (ciprofloxacin), aminoglycosides (gentamicin and amikacin), and β-lactams with inhibitors (piperacillin-tazobactam).

### Data analysis

Statistical analyses were performed by calculating the odds ratios (ORs) with the Mantel-Hansel test at 95% confidence interval (CI) and 5% significance level ($p \leq 0.05$) to compare patients infected by MDRPA and non-MDRPA strains. Forest plots were produced using Review Manager 5.0[19].

## RESULTS

As shown in **Figure 1**, a total of 2,677 articles were retrieved, 2,077 of which were excluded after title and abstract evaluation,

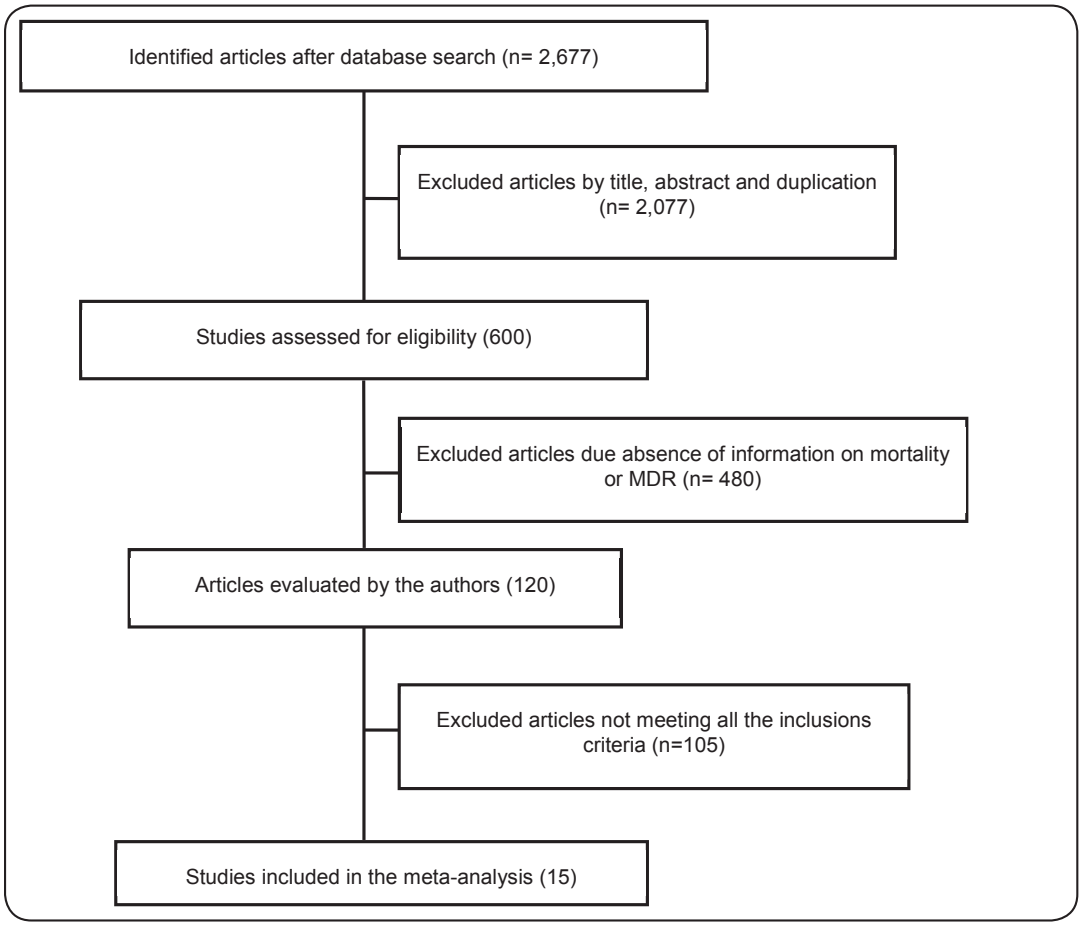


**FIGURE 1:** Schematic diagram of study selection. **MDR:** multidrug-resistant.

as well as because of duplication. In the second screening, 480 studies were excluded for their lack of information related to mortality and MDR and/or MBL detection; the remaining 120 articles were fully evaluated by the investigators. Finally, 15 studies matching the inclusion criteria were selected for analysis. The main characteristics of the 15 studies included in the meta-analysis are summarized in **Table 1**. The articles were published between 2006 and 2016, with a sample size comprising 3,201 *P. aeruginosa* isolates from five countries. Most of the studies were retrospective in design. The main sample source was bloodstream infection (BSI) and 30-day mortality was the outcome of interest.

The meta-analysis illustrated in **Figure 2** revealed a higher proportion of deaths among patients with MDRPA (44.65%, 363/813) compared to that in patients with non-MDRPA infections (24.8%, 593/2,388) (OR 2.39, 95% CI 1.70-3.36, $p$ <0.00001). Despite the substantial statistical heterogeneity ($I^2$ = 66%), only the study by Peña[20] presented results in favor of the non-MDRPA group; however, their results were not statistically significant (OR 0.82, 95% CI 0.35-1.97), which was possibly because they used the severity of the acute illness as the main predictor for mortality rather than the presence of an MDR isolate.

As presented in **Figure 3**, the risk of mortality in the non-SPM-1 group was four times greater than that observed in the SPM-1 group. However, the difference was not statistically significant ($p$ = 0.43), and there was great heterogeneity between the studies ($I^2$ = 82%) caused by Gomes[2] as a result of clinical and methodological differences among the investigations.

**TABLE 1:** Description of the studies included in the meta-analysis.

| Study | Study period | Country | Study design | Setting | Mortality Outcome (days) | Mortality by MDRPA (%) | Mortality by non-MDRPA (%) | Source of infection | Confounding factors control |
|---|---|---|---|---|---|---|---|---|---|
| Zawaski et al, 2006 | Sep 2004-Jun 2005 | Brazil | PO | Two tertiary hospitals | 30 | 51.2 | 37.6 | BSI | No |
| Furtado et al, 2009 | Jan 2003-Dec 2004 | Brazil | CC | University hospital | 30 | 49.0 | 33.0 | RTI | No |
| Tam et al, 2010 | Jan 2005-Dec 2008 | USA | RC | Two university hospitals | 30 | 40.0 | 11.9 | BSI | No |
| Caselli et al, 2010 | Jan 2000-Oct 2008 | Italy | RC | 12 hospital centers | 30 | 35.9 | 12.5 | BSI | No |
| Gomes et al, 2011 | Apr 2002 -Feb 2007 | Brazil | PC | University hospital | 30 | 73.3 | 3.8 | BSI, UTI, RTI | No |
| Joo et al, 2011 | Oct 2006-Mar 2009 | South Korea | PC | Tertiary university hospital | 30 | 38.1 | 21.9 | BSI | No |
| Trecarich et al, 2011 | Jan 2009-Sep 2010 | Italy | PC | Nine tertiary hospitals | 30 | 40.7 | 9.1 | BSI | No |
| Tumbarello et al, 2011 | Jan 2006-Dec 2007 | Italy | RC | Two university hospitals | 21 | 50.0 | 39.4 | BSI | No |
| Hirsch et al, 2012 | Jan 2007-Dec 2009 | USA | PC | Tertiary hospital | 30 | 46.1 | 10.3 | BSI | No |
| Morata et al, 2012 | Jan 2000- Dec 2008 | Spain | RC | University hospital | 30 | 32.3 | 17.0 | BSI | No |
| Peña et al, 2012 | Jan 2008 -Dec 2009 | Spain | RC | Multicenter (10 hospitals) | 30 | 35.2 | 27.1 | BSI | No |
| Peña et al, 2013 | Jan 2006-Dec 2011 | Spain | RC | Tertiary university hospital | 30 | 50.0 | 54.8 | RTI | No |
| Araujo et al, 2016 | May 2009-Dec 2012 and Apr-Oct 2014 | Brazil | CC | University hospital | 30 and 5 | 43,7 | 40.7 | BSI | No |
| Matos et al, 2016 | Jan 2010-Dec 2012 | Brazil | RC | Teaching hospital | 30 | 70.0 | 55.9 | BSI, UTI, RTI | No |

**MDRPA:** multidrug-resistant *Pseudomonas aeruginosa*; **non-MDRPA**: non-multidrug-resistant *Pseudomonas aeruginosa*; **PO:** prospective observational; **CC:** case control; **RC:** retrospective cohort; **PC**: prospective cohort; **BSI:** bloodstream infection; **RTI:** respiratory tract infection; **UTI:** urinary tract infection.

| Study | MDR | | Non-MDR | | Weight (%) | Odds ratio |
|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | M-H, random, 95% CI |
| Araújo 2016 | 42 | 54 | 68 | 2,012 | 7.8 | 7.41 [3.67, 14.98] |
| Caseli 2010 | 14 | 39 | 11 | 88 | 6.4 | 3.92 [1.58, 9.73] |
| Dantas 2014 | 24 | 57 | 26 | 63 | 7.6 | 1.03 [0.50, 2.14] |
| Furtado 2009 | 31 | 63 | 61 | 182 | 8.7 | 1.92 [1.07, 3.44] |
| Gomes 2011 | 11 | 15 | 1 | 26 | 1.8 | 68.75 [6.87, 687.92] |
| Hirsch 2012 | 6 | 13 | 17 | 150 | 4.7 | 6.71 [2.02, 22.30] |
| Joo 2011 | 16 | 42 | 35 | 160 | 7.6 | 2.20 [1.06, 4.55] |
| Matos 2016 | 14 | 20 | 20 | 34 | 4.9 | 1.63 [0.50, 5.29] |
| Morata 2012 | 41 | 127 | 100 | 582 | 9.9 | 2.30 [1.50, 3.53] |
| Peña 2012 | 51 | 145 | 132 | 487 | 10.1 | 1.46 [0.98, 2.17] |
| Peña 2013 | 30 | 60 | 17 | 31 | 6.6 | 0.82 [0.35, 1.97] |
| Tam 2010 | 8 | 25 | 10 | 84 | 5.4 | 3.48 [1.20, 10.14] |
| Trecarichi 2011 | 11 | 27 | 1 | 11 | 2.0 | 6.88 [0.77, 61.69] |
| Tumbarello 2011 | 20 | 40 | 26 | 66 | 7.2 | 1.54 [0.70, 3.40] |
| Zawaski 2005 | 44 | 86 | 68 | 212 | 9.3 | 2.22 [1.33, 3.70] |
| **Total (95% CI)** | | **813** | | **2,388** | **100.0** | **2.39 [1.70, 3.36]** |
| Total events | 363 | | 593 | | | |
| Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 41.01$, df = 14 (P= 0.0002); $I^2 = 66\%$ | | | | | | |
| Test for overall effect: Z = 5.04 (P < 0.00001) | | | | | | |

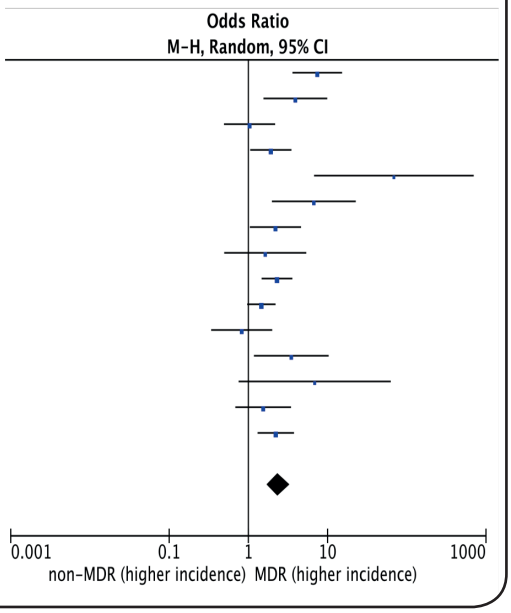


**FIGURE 2:** Forest plot of the association between MDR and the risk of mortality in patients with *Pseudomonas aeruginosa* infection. **MDR:** multidrug-resistant; **non-MDR**: non-multidrug-resistant; **M-H:** Mantel-Haenszel; ***random:*** *random* effect model; **95% CI:** 95% confidence interval.

| Study | MDR | | Non-MDR | | Weight (%) | Odds ratio |
|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | M-H, random, 95% CI |
| Araújo 2016 | 57 | 79 | 0 | 5 | 31.7 | 28.11 [1.49, 529,52] |
| Gomes 2011 | 12 | 34 | 5 | 7 | 36.9 | 0.22 [0.04, 1.30] |
| Matos 2016 | 33 | 50 | 0 | 4 | 31.4 | 17.23 [0.88, 338.64] |
| **Total (95% CI)** | | **163** | | **16** | **100.0** | |
| Total events | 102 | | 5 | | | |
| Heterogeneity: $Tau^2 = 7.72$; $Chi^2 = 11.27$, df = 2 (P= 0.004); $I^2 = 82\%$ | | | | | | |
| Test for overall effect: Z = 0.78 (P < 0.43) | | | | | | |

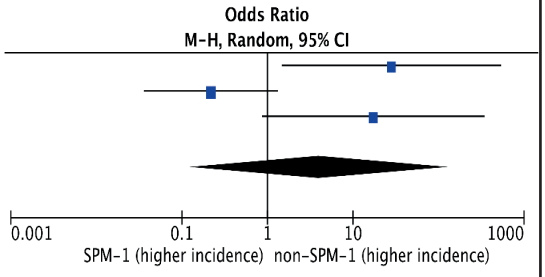


**FIGURE 3:** Forest plot of the association between MBL-producing and non-MBL-producing strains and the risk of mortality in patients with *Pseudomonas aeruginosa* infection. **MDR:** multidrug-resistant; **non-MDR**: non-multidrug-resistant; **M-H:** Mantel-Haenszel; ***random:*** *random* effect model; **95% CI:** 95% confidence interval; **MBL:** metallo-beta-lactamase; **non-MBL**: non-metallo-beta-lactamase; **SPM-1:** São Paulo-metallo-ß-lactamase-1; **non-SPM-1:** non-São Paulo-metallo-ß-lactamase-1.

## DISCUSSION

This study selected several original articles for analysis, combining and performing a synthesis of the results based on variables associated with MDRPA and relating them to mortality. The meta-analysis of the data revealed that *P. aeruginosa* infections resulted in high mortality rates in cases of infection with MDRPA compared to those of non-MDRPA infections. *P. aeruginosa* infections are opportunistic and are considered to have a high mortality in a global context. This pathogen is closely related to nosocomial infections in critically ill patients, but it also affects immunocompetent individuals[3,20-22].

Most of the selected studies focused on the bloodstream as the main site of infection. BSIs increase the costs to the hospital and the complexity of cases; they may prolong hospitalization and are often exacerbated by unfavorable outcomes. A study conducted at the teaching hospital in Pará State, Northern Brazil identified BSI as the most frequent route of infection among inpatients in intensive care units (ICU)[10]. A similar scenario was reported in India, wherein 48.2% of 593 blood cultures was determined to be positive for *P. aeruginosa*, 63.6% of which were MDR; this also highlights the increasing occurrence of MBL in the region, representing a major therapeutic problem[23].

Among the selected works, none assessed neonatal inpatients exclusively. Considering the peculiarity of the neonatal ICU population, there were few reports in the literature regarding the behavior of these resistant microorganisms. Life support of these patients requires both direct and indirect special care, aside from presenting critical immunosuppression and possible prolonged hospitalization[24]. However, a study conducted in 12 hospital centers of hematology and oncology in Italy described a retrospective series of nine years of BSI with *P. aeruginosa* in children diagnosed with cancer in pediatric oncology. The mortality rate reported in this study was 35.9% in cases of infection with MDRPA. This investigation emphasized that infection with this pathogen is a major concern in patients undergoing chemotherapy despite empirical antibiotic therapy containing at least one active drug, and that multidrug resistance is the greatest risk factor for a fatal outcome[25].

Although heterogeneous, the studied populations presented common aspects, including immunosuppression, underlying disease, use of immunosuppressive agents, antimicrobial therapy, inadequate empirical therapy, use of invasive procedures, and patient age range. Aside from infection with MDRPA, the main clinical features observed in the studies were HIV-positive patients with various complications, hematologic malignancy, cystic fibrosis, use of mechanical ventilation, and neonatal patients. The test of inconsistency showed a partial heterogeneity ($I^2 = 66\%$) between studies[2,3,26-29].

Zavascki et al.[8] reported that patients with infections by MBL-producing *P. aeruginosa* have higher mortality rates than those infected with non-MBL-producing strains, emphasizing the importance of appropriate initial antimicrobial therapy to reduce mortality rates. Exposure to antimicrobial agents predisposes patients to infection by MDRPA strains, and this selective pressure has contributed to the increase and spread of this pathogen, as well as the expression of different resistance genes[3,5,8,12,13].

The data in **Figure 3** show controversial results regarding the risk of death among patients infected with SPM-1-producing strains, as seen in the three studies that investigated this aspect[2,10,21]. Our database search identified many studies that lacked information regarding the detection of MBL (*bla*SPM-1) and mortality, preventing a more concrete analysis; with the increasing prevalence of SPM-1-producing strains in different regions, particularly in Brazil, this demonstrates the need for investigations with representative sample sizes for analysis[5,8,10,14,15].

In conclusion, the results of our study indicate a significantly higher mortality among patients infected with MDRPA compared to those infected with non-MDRPA, especially patients with BSI, immunosuppression, and inadequate antimicrobial therapy. However, the lack of published studies on the molecular aspects of *bla*SPM-1 detection limited the analysis and its association with mortality; therefore, our results should be interpreted with caution. Heterogeneity of the populations from the studies in this meta-analysis was observed because of the particular characteristics of each setting, especially for the condition of immunosuppression caused by different co-morbidities. Our findings highlight the need for additional studies on the molecular aspects of resistance and the peculiarities of different nosocomial settings.

**Conflict of interest**

The authors declare that there is no conflict of interest.

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