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A meta-analysis of antibiotic resistance rates in *Pseudomonas aeruginosa* isolated in blood cultures in Turkey between 2007 and 2017

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ABSTRACT

OBJECTIVE: The prevalence of *Pseudomonas aeruginosa* has remained stable in recent years, and resistant strains has increased dramatically. In this meta-analysis, we aimed to analyze the *P. aeruginosa* strains isolated from blood cultures in Turkey during the last 11 years and to reveal their antimicrobial susceptibility.

METHODS: Data collected between 2007 and 2017 were divided into two groups as Group-1; 2007–2011 and Group-2; 2012–2017. The differences in antibiotic resistance rates between Group-1 and Group-2 were analyzed. The study data were included according to PRISMA criteria, then meta-analysis was performed.

RESULTS: A total of 30 study data from 25 studies were included in the study. The prevalence rate of meropenem (MEM) resistance in *P. aeruginosa* in Turkey was 25.1% (95% CI: 20.65–29.83) according to a meta-analysis of 637 isolates. MEM resistance rates in Group-1 and Group-2 were 23.4% (95% CI: 18.34–28.99) and 29.3% (95% CI: 21.23–38.23), respectively. The prevalence rate of imipenem (IMP) resistance in *P. aeruginosa* in Turkey was 26.8% (%95CI: 23.40–30.35) according to a meta-analysis of 1421 isolates. IMP resistance rates in Group-1 and Group-2 were 26.2% (95%CI: 22.41–30.27) and 28.4% (95%CI: 21.57–35.88), respectively. Ciprofloxacin (CIP) resistance rate was 27.04% (95% CI: 21.88–32.52) in 1388 isolates. CIP resistance rates in Group-1 and Group-2 were 30.8% (95% CI: 24.35–37.56) and 18.6% (95% CI: 10.72–28.11), respectively. The prevalence rate of piperacillin-tazobactam (TZP) resistance in *P. aeruginosa* in Turkey was 29.2% (95% CI: 21.058–38.088) according to a meta-analysis of 1030 isolates. TZP resistance rates in Group-1 and Group-2 were 26.1% (95% CI: 17.76–35.31) and 38.2% (95% CI: 18.48–60.27), respectively.

CONCLUSION: There is a remarkable increase in resistance rates in *P. aeruginosa* to MEM and TZP in Turkey due to frequent use. Other antibiotics with antipseudomonal effect should be prioritized in the treatment of these infections.

Keywords: Antibiotic resistance; blood culture; bloodstream infections; carbapenems; Pseudomonas aeruginosa.

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Pseudomonas aeruginosa, a member of the Pseudomonadaceae family, is a Gram-negative opportunistic bacillus. *P. aeruginosa* exists in environments such as the soil and water, and also in live environments such as plant and animal tissues. It may cause life-threatening infections such as ventilator-associated pneumonia, sepsis, urinary system infections, gastrointestinal tract infections, skin, and bone-joint infections [1].

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Inadequate infection control measures and inappropriate use of antibiotics are considered to lead to an increase in antibiotic resistance rate in Pseudomonas spp.; and this acquired antimicrobial resistance restricts treatment options and makes the treatment of infections difficult. Antimicrobial resistance in *P. aeruginosa* is divided into intrinsic and acquired resistance. Intrinsic resistance includes a variety of mechanisms such as reduction in outer membrane permeability, expression of outflow pumps, and production of antibiotic inactivating enzymes [1, 2]. Acquired resistance results from the acquisition of external genes responsible for resistance through horizontal gene transfer and chromosomal gene mutations [1].

Frequent use of carbapenems in the treatment of *P. aeruginosa* infections causes carbapenem resistance. This is achieved by reduced permeability (loss of porin OprD), overexpression of outflow systems, and the production of carbapenemase (metallo-beta-lactamase) [3].

It is noteworthy that the prevalence of *P. aeruginosa* has remained stable in recent years, with a dramatic increase in the prevalence of resistant strains [4]. In this meta-analysis, we o analyzed *P. aeruginosa* strains isolated from blood cultures in Turkey during the past 11 years and to reveal their antimicrobial susceptibility. *P. aeruginosa* can be colonized in urine, sputum, tracheal aspirate, and catheters. We included isolates only from blood cultures to exclude colonization and contamination and to reveal the resistance rates in *P. aeruginosa* strains causing real infections.

Highlight key points

- One of the most important problems encountered in the treatment of bacteremia caused by *P. aeruginosa* is the increasing rate of antibiotic resistance.
- The resistance rates against meropenem and piperacillin-tazobactam, which are commonly used antibiotics in the treatment of *P. aeruginosa*, have been significantly increased in the last five years in Turkey.
- On the other hand, there has been a decrease in the resistance rates of ciprofloxacin, amikacin and gentamicin in the last five years.

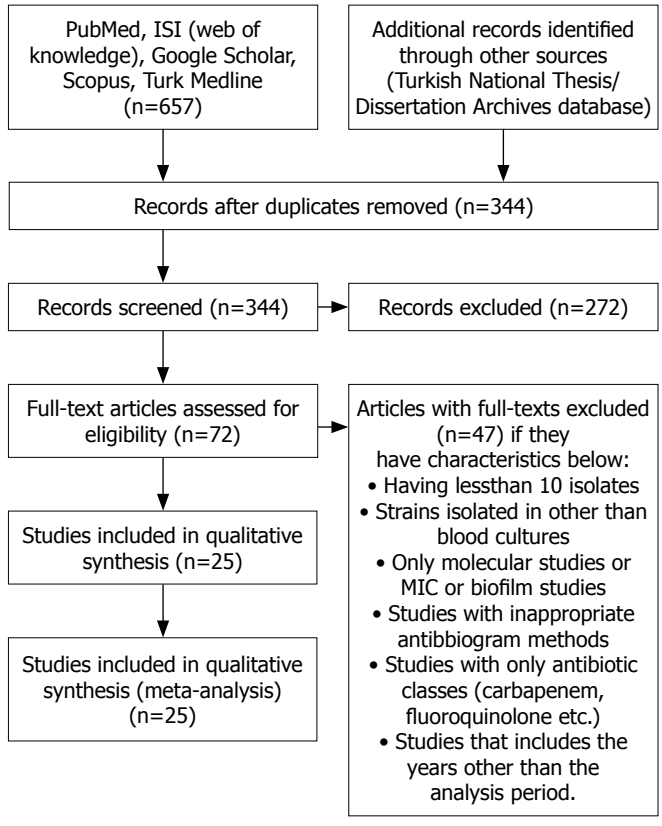

FIGURE 1. Schematic flow diagram describing the study design.

MATERIALS AND METHODS

Data Search

In this meta-analysis, the searches were performed by writing of the words "*P. aeruginosa*,""blood culture; and also kan kulturu," in Turkish, "bacteremia; and also bakteriyemi" in Turkish, "sepsis," "Turkey; and also, Turkiye" as the keyword on Google Scholar, PubMed, Web of Science, Turkish Medline, and Higher Educational Institution of Turkey thesis center databases. The reference list of publications included in the study was also scanned. Screening was performed by two researchers (SAI and RAC) in September and October 2018.

Inclusion and Exclusion Criteria

Original researches with *P. aeruginosa* species isolated from blood cultures in Turkey between 2007 and 2017 were included in the study. Original articles with study data are verifiable in terms of numbers and rates, those with at least 10 isolate data, and with full text in Turkish or English were recorded. Studies were required to use the Clinical and Laboratory Standards Institute and/or European Committee on Antimicrobial Susceptibility Testing criteria during antibiotic resistance testing. Other exclusion criteria are presented in Figure 1.

Literature Search and Collection of Data

The conformity of the articles was cross-checked by two independent researchers and the data were documented. Disputes between those who gathered work data were resolved through discussion and consultation with third author (EY). Information about author surname, date of publication, years of collection of isolates, number of isolates, number (n) and ratio (%) of resistant isolates, and cities where the isolates were collected were recorded.

Two groups were formed in the study according to the years of data collection to reveal the temporal change in the antibiotic resistance rates; the first group included the years between 2007 and 2012 and the second group between 2013 and 2017. Studies containing both study intervals were divided into the two groups according to the number of isolates.

Antibiotics were classified as Group A; ceftazidime (CAZ), gentamicin (GN), and piperacillin-tazobactam (TZP), Group B; amikacin (AK), aztreonam (ATM), cefepime (FEP), ciprofloxacin (CIP), levofloxacin (LEV), imipenem (IMP), and meropenem (MEM), according to the CLSI M100-ED28: 2018 Performance Standards for Antimicrobial Susceptibility Testing [5]. Piperacillin was classified under the other antibiotic group.

Statistical Analysis

Study design was created through the Medical Research Support (MedicReS) e-picos assistant program. The data included in the study were recorded in the Microsoft Office 2016 Professional Plus Excel program. The data were sorted by years in Excel program. The MedCalc© software version 17.9.7 program was used for meta-analysis. Author surnames, total number of isolates, and the number of isolates resistant to antibiotics indicated in the Antibiotic Stewardship Programs (ASP) were transferred from excel to MedCalc © for analysis. During the process of analysis, the 10-year period data between 2007 and 2017 were first obtained. Second, the period between 2007 and 2012 was classified as Group 1, whereas 2013 and 2017 were classified as Group 2; the change in antibiotic resistance rates was then analyzed over 5-year periods.

The statistical test for heterogeneity was performed to measure the heterogeneity of the data. The I-squared (I^2 Inconsistency) and Cochran's Q tests were used to determine the inconsistency and heterogeneity among the studies. Moreover, the meta-regression analysis was used to test the heterogeneity among year's subgroups. Accordingly, $I^2 \leq 25\%$ heterogeneity was assumed to be insignificant and the fixed effect was used. An $I^2 > 25\%$ heterogeneity value was assumed to be significant; the study data were considered as nonhomogeneous hence the random effect value was used. $P < 0.01$ was considered to indicate that there was no need to add more studies, while $0.01 < p < 0.05$ was found to be statistically significant but it was accepted that the results could change if new studies were to be added.

The Beg's funnel plot was used to evaluate possible bias and the results were interpreted according to Oxford's Catalogue of Bias:

1. Information bias: Authors of the studies included in our analysis were not informed that they would be included in the meta-analysis. All articles were analyzed retrospectively
2. Attrition bias: The studies included in our analysis are not clinical studies, but are retrospective studies based on laboratory data. Therefore, there is no question bias
3. Confounding bias: The literature search was performed in five different databases and all articles which met the inclusion criteria were included in the analysis. The confounding bias analysis could not be performed because these articles were not randomized controlled studies
4. Selection bias: Measures for selection bias are difficult in observational studies. Exclusion criteria of the studies included in the analysis and the randomness of the selected cases was evaluated. This bias was not found in the studies. However, there may be articles which have not yet been published, although they are covered by years of study, or the full text of some works may not be available for other reasons. It should be kept in mind that different phenotypic and genotypic methods can be used in the included studies
5. Detection bias: *P. aeruginosa* isolates included in our meta-analysis were mostly obtained from patients treated in intensive care units. Although this cannot be considered as a detection bias, it should be noted that antibiotic resistance rates may be higher in this meta-analysis. Maximum care should be taken when comparing resistance rates to non-bloodstream infection isolates.

RESULTS

In our study, we came across 658 articles in accordance with the keywords mentioned in the criteria (Fig. 1).

TABLE 1. MEM resistance rates in *P. aeruginosa* in Turkey according to the years included in meta-analysis [6, 8–19]

Author surname/publication date/isolates year	Total (2007–2017)					Group 1 (2007–2012)			Group 2 (2013–2017)		
	Sample size	Resistance rates (%)	95% CI	Weight		Sample size	Resistance rates (%)	95% CI	Sample size	Resistance rates (%)	95% CI
				Fixed	Random						
Coskun/2018/2016–2017	41	26.8	14.221–42.944	41	26.8	N/A	N/A	N/A	41	26.8	14.221–42.944
Celik/2013/2007–2010	85	17.6	10.227–27.430	85	17.6	85	17.6	10.227–27.430	N/A	N/A	N/A
Celik/2013/2011–2012	43	25.6	13.519–41.172	43	25.6	43	25.6	13.519–41.172	N/A	N/A	N/A
Colakoglu/2014/2012	20	5.0	0.127–24.873	20	5.0	20	5.0	0.127–24.873	N/A	N/A	N/A
Colakoglu/2014/2014	16	18.7	4.047–45.646	16	18.7	N/A	N/A	N/A	16	18.7	4.047–45.646
Duman/2011/2009	19	10.5	1.301–33.138	19	10.5	19	10.5	1.301–33.138	N/A	N/A	N/A
Er/2015/2011–2013	31	32.2	16.682–51.373	31	32.2	N/A	N/A	N/A	31	32.2	16.682–51.373
Guney/2011/2008–2009	46	26.1	14.267–41.132	46	26.1	46	26.1	14.267–41.132	N/A	N/A	N/A
Kocaoglu/2017/2014–2016	18	16.7	3.579–41.418	18	16.7	N/A	N/A	N/A	18	16.7	3.579–41.418
Kucukates/2016/2013–2014	11	18.2	2.283–51.776	11	18.2	N/A	N/A	N/A	11	18.2	2.283–51.776
Kucukbasmaci/2007/2007	55	21.8	11.814–35.010	55	21.8	55	21.8	11.814–35.010	N/A	N/A	N/A
Sirin/2017/2012–2015	40	45.0	29.259–61.509	40	45.0	N/A	N/A	N/A	40	45.0	29.259–61.509
Wilke/2011/2008	31	12.9	3.630–29.834	31	12.9	31	12.9	3.630–29.834	N/A	N/A	N/A
Wilke/2011/2009	37	37.8	22.458–55.243	37	37.8	37	37.8	22.458–55.243	N/A	N/A	N/A
Wilke/2011/2010	54	33.3	21.092–47.474	54	33.3	54	33.3	21.092–47.474	N/A	N/A	N/A
Yilmaz/2010/2008	13	23.1	5.038–53.813	13	23.1	13	23.1	5.038–53.813	N/A	N/A	N/A
Yilmaz/2013/2009–2010	77	29.9	19.967–41.378	77	29.9	77	29.9	19.967–41.378	N/A	N/A	N/A
Total (fixed effects)	637	25.5	22.209–29.033	637	25.5	480	23.9	20.285–28.028	157	30.2	23.299–37.910
Total (random effects)	637	25.1	20.655–29.838	637	25.1	480	23.5	18.348–28.999	157	29.4	21.236–38.232
Q			28.3269				18.8200			7.0898	
DF			16				10			5	
Significancelevel (p)			**0.0289**				**0.0426**			0.2140	
I^2 (inconsistency)			43.52%				46.87%			29.48%	
95% CI for I^2			0.00–68.10				0.00–73.55			0.00–71.16	

MEM: Meropenem; CI: Confidence interval.

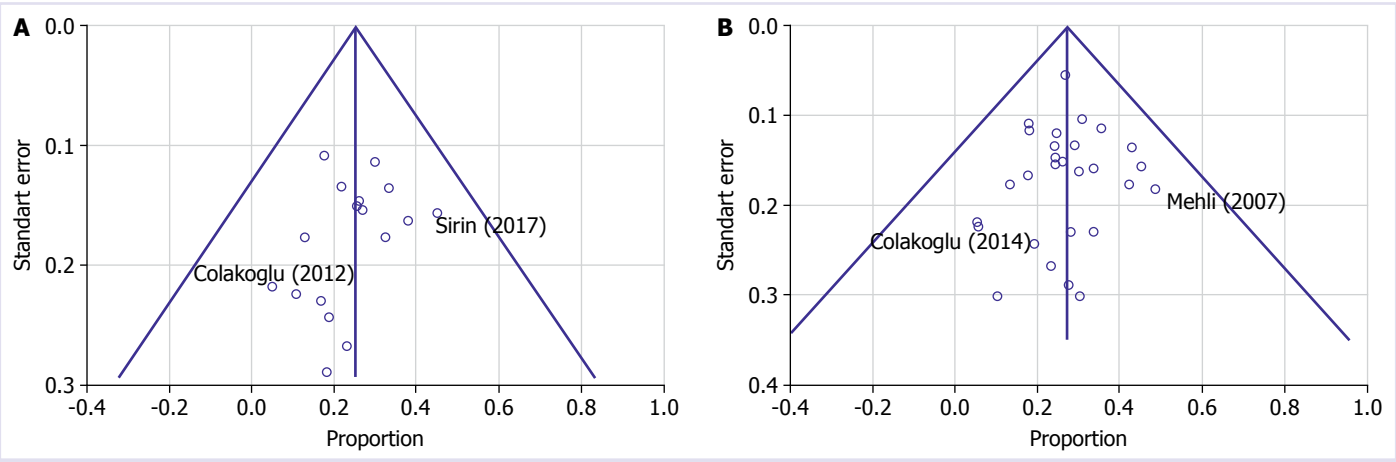

FIGURE 2. Beg's funnel plot of the studies in the meta-analysis [6–8].

Three hundred and fourteen articles which were found to be repetitive in different databases were excluded from the study. After examining the manuscripts and abstracts of 344 articles, 272 articles were not included in the analysis. Forty-seven of the 72 articles whose full texts could be obtained did not meet the inclusion criteria. Finally, 30 study data in 25 studies were included in our meta-analysis (Fig. 1). Of the 1421 isolates included in the study, 318 were strains from intensive care units, while 245 strains were from non-intensive care units. Data on the remaining 858 strains were not available.

According to our analysis, all the studies conducted in Turkey were retrospective. Studies about the resistance rates in *P. aeruginosa* isolated in blood cultures were mostly conducted in the provinces of Izmir (n: 3) and Istanbul (n: 3). Two studies from each province of Ankara, Gaziantep, and Konya and one study from each province of Adana, Afyon, Amasya, Denizli, Diyarbakir, Duzce, Erzurum, Kahramanmaras, Kocaeli, Malatya, Sivas, Tokat, and Van were also included in the meta-analysis. The highest resistance rates were reported by Sirin et al. in Izmir for MEM, and by Mehli et al. in Gaziantep for IMP; the resistance rates were 45% and 48%, respectively (Fig. 2a, b) [6, 7]. The lowest MEM and IMP resistance rates were found to be 5% in the study of Colakoglu et al. [8] published in 2014 which include 2012 year data (Fig. 2a, b).

MEM resistance prevalence rate in *P. aeruginosa* in Turkey was 25.1% (95% Cl: 20.65–29.83) according to the meta-analysis of 637 isolates. In heterogeneity testing among the studies included, the Cochrane Q test was 28.3269 and I^2=98.77%. In addition, it was concluded that the analysis results were statistically significant (p=0.0289), however, the results could be affected by additional studies (Table 1 and Fig. 3) [6, 8–19]. Subgroup analysis in the time periods analyzed demonstrated that the MEM resistance rates in Group-1 and Group-2 were 23.4% (95% Cl: 18.34–28.99) and 29.3% (95% Cl: 21.23–38.23), respectively. The MEM resistance rate was found to have increased, however, we cannot comment on the significance of this increase due to the fact that the average value (23.46%) of Group-1 is within the confidence interval (21.23–38.23) of Group-2.

The IMP resistance prevalence rate in *P. aeruginosa* in Turkey was 26.8% (95% Cl: 23.40–30.35) according to a meta-analysis of 1421 isolates. In heterogeneity testing among studies included in the study, the Cochrane Q test was Q=53.4894 and I^2=47.65% (Table 2 and Fig. 4) [6–30]. Results of the analysis were found to be statistically significant (p=0.0026). Subgroup analysis in the time periods analyzed demonstrated that the IMP resistance rates in Group-1 and Group-2 were 26.2% (95% Cl: 22.41–30.27) and 28.4% (95% Cl: 21.57–35.88), respectively. The IMP resistance rate was found to have increased, however, we cannot comment on the significance of this increase due to the fact that the average value (26.2%) of Group-1 is within the confidence interval of Group-2.

The CIP resistance rate was reported as 27.04% (95% Cl: 21.88–32.52) in 1388 isolates and reduced from 30.76% (95% Cl: 24.35–37.56) in Group 1 to 18.62% (95% Cl: 10.72–28.11) in Group 2.

The FEP resistance rate was reported as 34.56% (95% Cl: 27.18–42.32) in 1175 isolates and reduced from 36.27% (95% Cl: 27.57–45.44) in Group 1 to 30.50% (95% Cl: 16.19–47.07) in Group 2.

TABLE 2. Imipenem resistance rates in *P. aeruginosa* in Turkey according to the years included in meta-analysis [6–30]

Author surname/publication date/isolates year	Total (2007–2017)					Group 1 (2007–2012)			Group 2 (2013–2017)		
	Sample size	Resistance rates (%)	95% CI	Weight		Sample size	Resistance rates (%)	95% CI	Sample size	Resistance rates (%)	95% CI
				Fixed	Random						
Bozkurt/2008/2007	10	30.0	6.674–65.245	0.8	1.5	10	30.0	6.674–65.245	N/A	N/A	N/A
Cosar/2009/2006–2007	56	28.6	17.295–42.210	3.9	4.4	56	28.6	17.295–42.210	N/A	N/A	N/A
Coskun/2018/2016–2017	41	24.4	12.363–40.305	2.9	3.7	N/A	N/A	N/A	41	24.4	12.363–40.305
Cakirlar/2017/2011–2014	339	26.5	21.923–31.589	23.4	7.2	339	26.5	21.923–31.589	N/A	N/A	N/A
Celik/2013/2011–2012	43	25.6	13.519–41.172	3.0	3.8	43	25.6	13.519–41.172	N/A	N/A	N/A
Celik/2013/2007–2010	85	17.6	10.227–27.430	5.9	5.2	85	17.6	10.227–27.430	N/A	N/A	N/A
Colakoglu/2014/2014	16	18.7	4.047–45.646	1.2	2.1	N/A	N/A	N/A	16	18.7	4.047–45.646
Colakoglu/2014/2012	20	5.0	0.127–24.873	1.4	2.4	20	5.0	0.127–24.873	N/A	N/A	N/A
Dagi/2011/2008–2009	92	30.4	21.267–40.903	6.4	5.4	92	30.4	21.267–40.903	N/A	N/A	N/A
Duman/2011/2009	19	5.3	0.133–26.028	1.2	2.3	19	5.3	0.133–26.028	N/A	N/A	N/A
Er/2015/2011–2013	31	41.9	24.548–60.924	2.2	3.2	N/A	N/A	N/A	31	41.9	24.548–60.924
Gultekin/2014/2011–2013	70	24.3	14.829–36.012	4.90	4.8	35	22.8	10.421–40.136	35	25.7	12.489–43.256
Guney/2011/2008–2009	46	23.9	12.586–38.767	3.24	4.0	46	23.9	12.586–38.767	N/A	N/A	N/A
Kilinc/2015/2014–2015	35	17.1	6.562–33.650	2.48	3.4	N/A	N/A	N/A	35	17.1	6.562–33.650
Kocaoglu/2017/2014–2016	18	27.8	9.695–53.480	1.31	2.2	N/A	N/A	N/A	18	27.8	9.695–53.480
Kucukates/2016/2014–2016	11	27.3	6.022–60.974	0.83	1.6	N/A	N/A	N/A	11	27.3	6.022–60.974
Kucukbasmaci/2007/2007	55	23.6	13.228–37.020	3.86	4.3	55	23.6	13.228–37.020	N/A	N/A	N/A
Mehli/2007/2007	29	48.3	29.449–67.469	2.07	3.0	29	48.3	29.449–67.469	N/A	N/A	N/A
Ozkaya/2015/2012–2014	10	10.0	0.253–44.502	0.76	1.5	N/A	N/A	N/A	10	10.0	0.253–44.502
Sahin/2013/2009–2010	18	33.3	13.343–59.007	1.31	2.23	18	33.3	13.343–59.007	N/A	N/A	N/A
Sirin/2017/2012–2015	40	45.0	29.259–61.509	2.83	3.7	N/A	N/A	N/A	40	45.0	29.259–61.509
Temiz/2014/2012	13	23.1	5.038–53.813	0.97	1.8	13	23.1	5.038–53.813	N/A	N/A	N/A
Uzun/2012/2011	73	17.8	9.837–28.525	5.10	4.91	73	17.8	9.837–28.525	N/A	N/A	N/A
Wilke/2011/2008	31	12.9	3.630–29.834	2.21	3.18	31	12.9	3.630–29.834	N/A	N/A	N/A
Wilke/2011/2009	37	29.7	15.873–46.980	2.62	3.53	37	29.7	15.873–46.980	N/A	N/A	N/A
Wilke/2011/2010	54	42.6	29.235–56.792	3.79	4.29	54	42.6	29.235–56.792	N/A	N/A	N/A
Yilmaz/2010/2008	13	23.1	5.038–53.813	0.97	1.77	13	23.1	5.038–53.813	N/A	N/A	N/A

CI: Confidence interval.

Table 2 (cont.). Imipenem resistance rates in *P. aeruginosa* in Turkey according to the years included in meta-analysis [6–30]

Author surname/publication date/isolates year	Total (2007–2017)			Weight		Group 1 (2007–2012)			Group 2 (2013–2017)		
	Sample size	Resistance rates (%)	95% CI	Fixed	Random	Sample size	Resistance rates (%)	95% CI	Sample size	Resistance rates (%)	95% CI
Yilmaz/2013/2009–2010	77	35.1	24.532–46.785	5.38	5.01	77	35.1	24.532–46.785	N/A	N/A	N/A
Yis/2015/2010–2011	39	33.3	19.088–50.217	2.76	3.63	39	33.3	19.088–50.217	N/A	N/A	N/A
Total (fixed effects)	1421	26.9	24.632–29.263	10000	100	1184	26.5	24.034–29.097	237	28.9	23.354–35.040
Total (random effects)	1421	26.8	23.406–30.353	100	100	1184	26.2	22.419–30.278	237	28.4	21.572–35.887
Q			53.4894				40.6012			12.3095	
DF			28				20			8	
Significance level (p)			**0.0026**				**0.0042**			0.1379	
I^2 (inconsistency)			47.65%				50.74%			35.01%	
95% CI for I^2			19.25–66.07				18.65–70.17			0.00–70.08	

CI: Confidence interval.

The resistance rates and changes in the rates in *P. aeruginosa* to the rest of the antibiotics in ASP arepresented in Table 3.

A negligible asymmetry was found in the funnel plot analysis of IMP and MEM, and the asymmetry test did not show any bias.

DISCUSSION

P. aeruginosa is one of the most important bacteria leading to community and hospital acquired life-threatening infections.It may even develop resistance to antibiotics even during treatment of these bacteria-related infections [31].

The antibiotic resistance rates and profiles may differ even between clinics and intensive care units within the same hospital.These differences can be observed between different regions of Turkey, or even different hospitals and different districts in the same city. Although there have been numerous studies on this subject, the antibiotic resistance rate of *P. aeruginosa* isolates in Turkey is uncertain.

According to the results of a meta-analysis from Turkey by Acar et al. [32], pooled resistance prevalence of *P. aeruginosa* to TZP, CAZ, FEP, MEM, IMP, CIP, GN, and AK was 33.9%, 38.6%, 35.6%, 30.1%, 28.0%, 30.7%, 28.2%, and 17.8%, respectively. The resistance rates in *P. aeruginosa* isolates were found to be higher in our study, when compared to the results of Acar et al. [32]. The most important reason for this difference was that Acar et al. included all isolates from urine, respiratory tract specimen, and wound, besides blood samples in their meta-analysis.

According to our meta-analysis, TZP, MEM, and IMP were the antibiotics against which *P. aeruginosa* showed increased resistance rates between the two study periods, by +12.17, +5.91, and +2.2 points, respectively. CIP, GN, and FEP were the antibiotics against which *P. aeruginosa* demonstrated reduced resistance rates between the two study periods by −12.14, −6.51, and −5.77 points, respectively. No remarkable changes were also shown for CAZ, AK, and LEV in *P. aeruginosa*. Similar to our study, results of the study by Acar et al. demonstrated that the highest increase in resis-

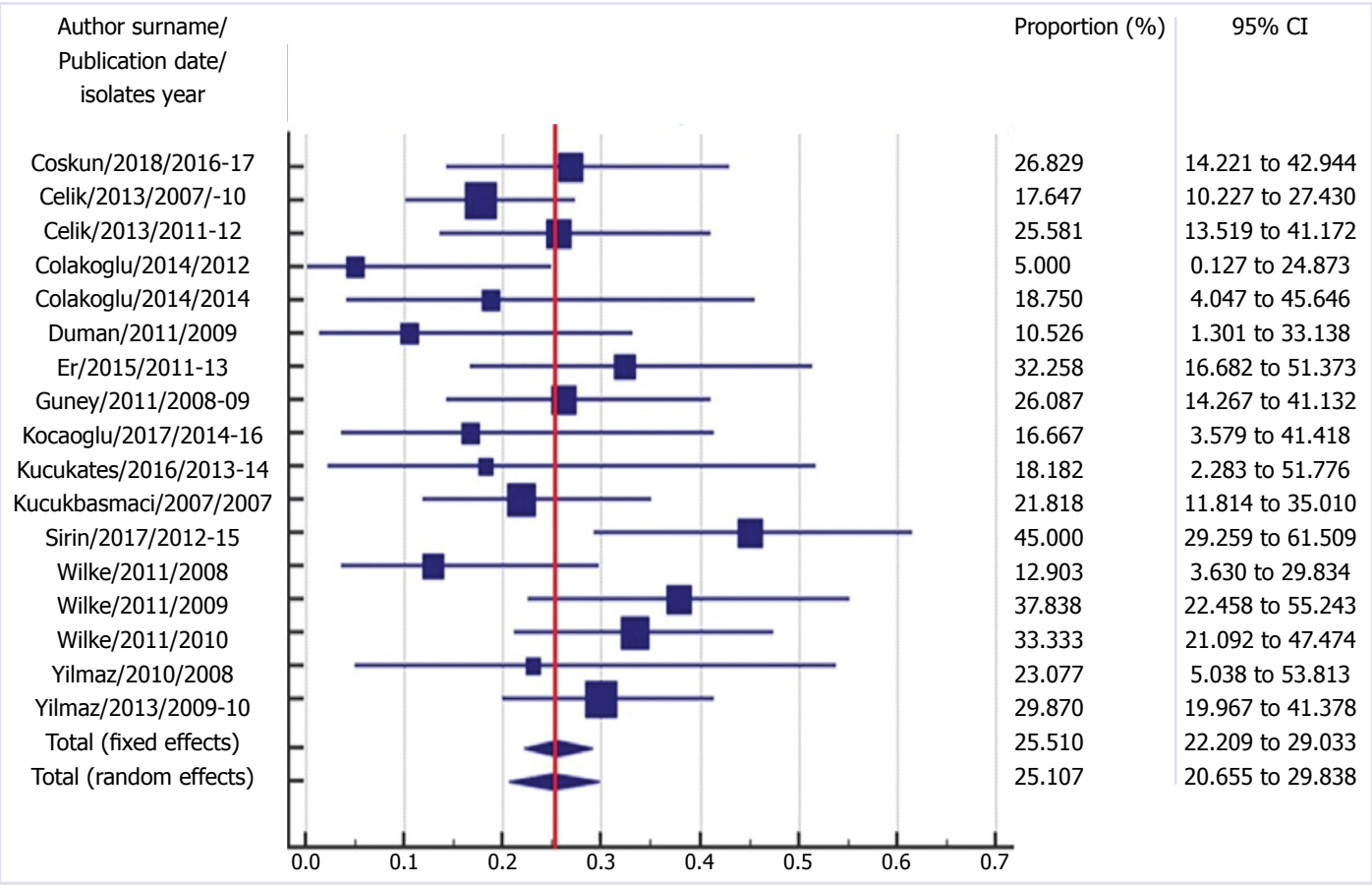

FIGURE 3. The overall meropenem resistance rates in *P. aeruginosa* in Turkey in studies included in meta-analysis [6, 8–19].

tance rates wasin MEM, IMP, and especially in TZP. [32]. Similarly, there was a decrease in resistance rates in CIP, GN, and FEP. This decrease was highest in CIP and negligible in FEP. These changes in resistant rates almost completely correlate with the rate of the antibiotic use in Turkey, except for CIP. TZP is the most common antibiotic used empirically in inpatient clinics in Turkey, therefore, it is reasonable for TZP to have a higher increase rate. The increase rate in MEM is remarkably higher than IMP, because MEM is the most commonly used carbapenem in Turkey. CAZ is rarely preferred as an antipseudomonal cephalosporin. Furthermore, clinicians avoid using AK because of its toxic effects. For this reason, we concluded that the reduced resistance rate of these antibiotics was due to the low rate of use. Although CIP is widely used in outpatient clinics and although we have one of the highest CIP resistance rates in Enterobacteriaceae in the world, we demonstrated that the resistance rate of CIP in *P. aeruginosa* decreased increasingly in recent years. Despite the absence of a clear explanation for this, we suggest that it may be due to the rare use CIP empirically in hospitals, although it is frequently used in public. Interestingly, we revealed lower CIP resistance rates than for both carbapenems in the meta-analysis. Our findings support the literature knowledge that the more you use an antibiotic, the more resistance rates you face.

In this meta-analysis, MEM resistance rate in *P. aeruginosa* as a cause of infection of the bloodstream in Turkey was found to be 25.1% and this rate was higher than 52.9% of all the study data. Sirin et al. in 2017 found that the MEM resistance in Izmir was 45% in 40 blood culture isolates and this study had the highest rate in our analysis. Although the resistance rate increased in Group 1 (29.3%), in the study of Sirin et al. [6], this rate was even higher than the MEM resistance rate in Group 2. The authors of the study attributed the high resistance rate in this study to the frequent empiric carbapenem use and to the conduction of the study only in the intensive care units. The lowest MEM resistance rate (5%) was reported by Colakoglu et al. [8] from Adana in the 2012 data of their study (n: 20). However, the same

Table 3. Antibiotic resistance rates in *P. aeruginosa* isolates according to ASP*

G**	A***	Resistance rate (%)								
		Total			Group 1 (2007–2012)			Group 2 (2013–2017)		
		Sample size	Resistance rates (%)	95% CI	Sample size	Resistance rates (%)	95% CI	Sample size	Resistance rates (%)	95% CI
A	CAZ	1374	35.2	28.259–42.472	1153	35.0	28.147–42.248	221	35.0	14.120–59.451
	GN	1210	23.3	17.532–29.643	1025	25.2	18.131–33.003	185	18.7	9.348–30.350
	TZP	1030	29.2	21.058–38.088	833	26.1	17.767–35.319	197	38.2	18.482–60.274
B	AK	1288	10.5	7.683–13.810	1068	10.8	7.657–14.524	220	9.9	3.881–18.349
	ATM	472	54.6	39.645–69.220	472	54.6	39.645–69.220	NA	NA	NA
	FEP	1175	34.6	27.189–42.325	956	36.3	27.579–45.441	219	30.5	16.193–47.075
	CIP	1388	27.0	21.888–32.526	1145	30.8	24.352–37.566	243	18.6	10.721–28.117
	LEV	269	21.1	13.453–29.978	161	21.1	15.116–28.089	108	20.1	5.629–40.565
	IMP	1421	26.8	23.406–30.353	1184	26.2	22.419–30.278	237	28.4	21.572–35.887
	MEM	637	25.1	20.655–29.838	480	23.5	18.348–28.999	157	29.4	21.236–38.232
Other	PIP	214	51.7	26.836–76.088	214	51.7	26.836–76.088	NA	NA	NA

CI: Confidence interval; *: Antibiotic stewardship programs; **: According to the CLSI M100-ED28: 2018 performance standards for antimicrobial susceptibility testing. ***: Antibiotics: Ceftazidime (CAZ), gentamicin (GN), piperacillin-tazobactam (TZP), amikacin (AK), aztreonam (ATM), cefepime (FEP), ciprofloxacin (CIP), levofloxacin (LEV), imipenem (IMP), meropenem (MEM), piperacillin (PIP).

study revealed a remarkable increase in MEM resistance (18.7%) in the 2014 data. Since the 2014 data werenot analyzed alone in our meta-analysis, there is no possibility to compare the MEM resistance rates of the 2014 data in this study with our results. However, it may be concluded that the MEM resistance rates in the study were still lower than those of our results, since the year of this study was included in Group-2 of our meta-analysis.

In Turkey, there is an increasing trend in resistance rate in *P. aeruginosa* strains to especially carbapenems [33]. According to the results of our meta-analysis, IMP resistance in *P. aeruginosa* strains was found to be 26.80% in Turkey during the past 10 years, and this rate was higher than 55.1% of all study data. Furthermore, a higher resistance rate was found in Group-2 compared to Group-1, 28.4% and 26.2%, respectively. Although it was included in Group-1, the highest resistance rate in all the years was reported by Mehli et al. [7] in their study conducted in Gaziantep in 2007. The authors of the study attributed the high resistance rate in this study to the prolonged hospital stay in the intensive care units and surgical departments due to complications and comorbidities, and to the high rate of non-compliance with antibiotic use protocols.

Multicenter studies are considered to be more useful in determining the antibiotic resistance rate of countries. Ergonul et al. [34] reported the carbapenem resistance rate in *P. aeruginosa* to be 43% in their multicenter study conducted in 17 intensive care units in Turkey in 2016. This study was not included in the meta-analysis since the resistance of IMP/MEM was not mentioned separately, and the presence of resistance to any of the IMP or MEM was considered as carbapenem resistance in the method section of this study. Although results in the study are not directly comparable to ours, carbapenem resistance rates in the study were higher than those of the IMP or MEM resistance rates in our meta-analysis.

In a study performed in between 2014 and 2017 years in Infectious Diseases and Clinical Microbiology Clinic in Turkey, examining bacteria isolated in blood cultures and their susceptibility, *P. aeruginosa* is found to be third most frequent among five isolates [35]. In this study, no resistance was detected against IMP. CIP and CAZ resistance was 20% when TZP resistance was 40%. These rates are less than the rates we determined in our analysis. The reason for this situation was thought to be the low number of isolates and the fact that the study was conducted in clinical patients.

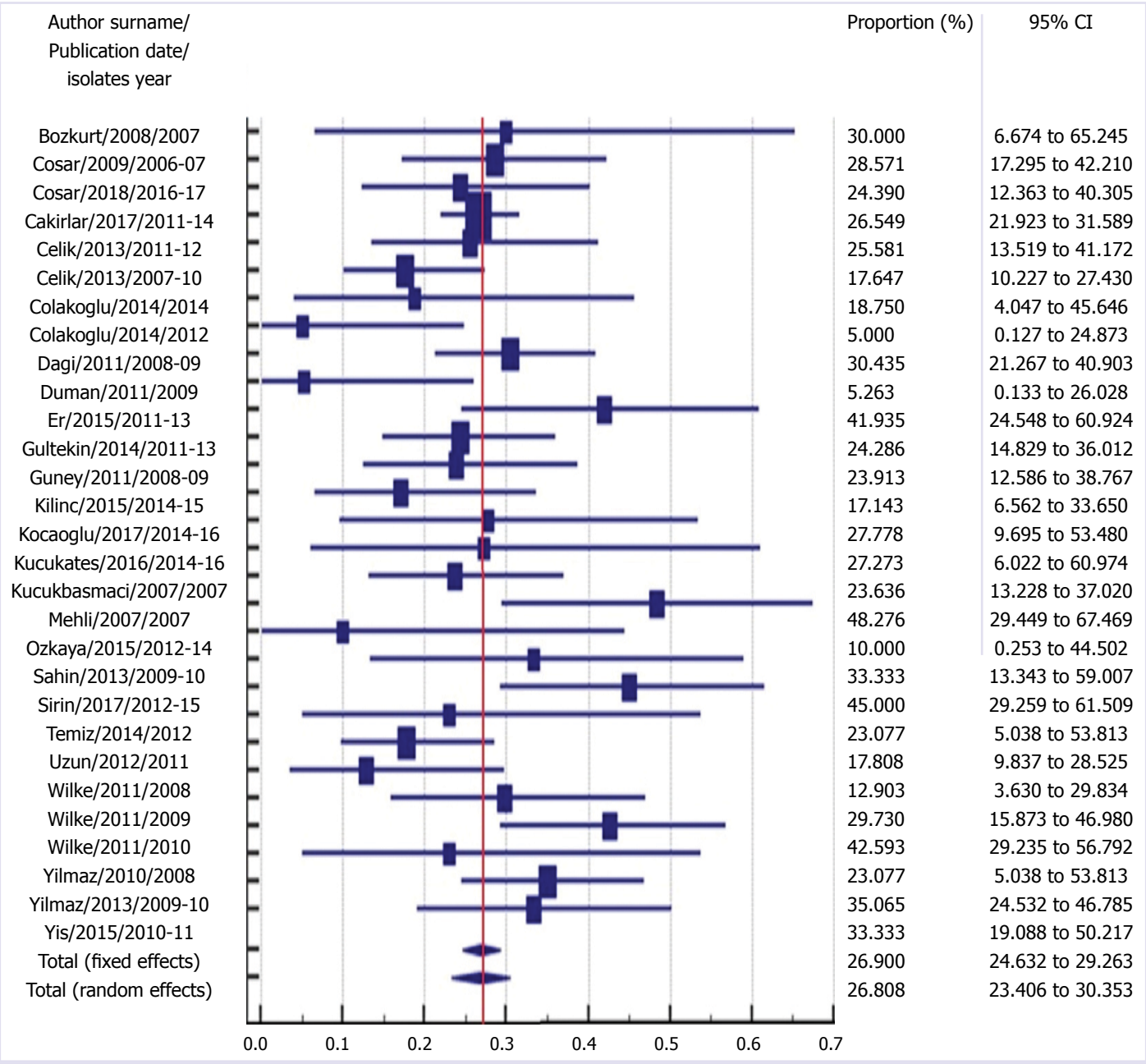

FIGURE 4. The overall imipenem resistance rates in *P. aeruginosa* in Turkey in studies included in meta-analysis [6–30].

The carbapenem resistance rate in invasive *P. aeruginosa* infections in EU/EEA countries was reported to be 17.4% by the European Centre for Disease Prevention and Control (ECDC) in 2017 [36]. This rate is lower than both the MEM and IMP resistance rates revealed in our analysis. According to EARS-Net data, Romania with the highest rate (63.4%), together with Croatia (30.7%), Hungary (36.6%), Greece (39.3%), Slovakia (47%), and Latvia (57.1%), were the EU/EEA countries with higher carbapenem resistance rates compared to Turkey. The lowest resistance carbapenem rate in *P. aeruginosa* among the EU/EEA countries was in Iceland (0%). In contrast with our meta-analysis, there has been a significant decrease in carbapenem resistance in EU/EEA countries between 2014 and 2017 according to the ECDC report.

The IMP resistance rates in *P. aeruginosa* in Iran and Russia, which are neighboring countries of Turkey, were higher than the rate in Turkey with 54% and 75.3%, respectively [37, 38]. The increase trend in resis-

tance rates to the Middle East and the east of Europe suggests that this situation is correlates with the level of development of countries, and there is a need for the development of strict infection control measures and antibiotic use protocols.

According to ECDC data between 2014 and 2017, the highest resistance rate in *P. aeruginosa* was against fluoroquinolones (20.3%); however, it was against ATM in Turkey according to our meta-analysis. Although this antibiotic is not in use in Turkey, further evaluation of the causes of the high resistance rate against ATM may be useful.In the study period corresponding to the period in the ECDC report (Group-2), Turkey has a lower CIP resistance rate and a similar LEV resistance rate compared to EU countries.According to EARS-Net 2017 data, TZP, CAZ, and aminoglycoside resistance were reported as 18.3%, 14.7%, and 13.2%, respectively.In addition, the resistance rates of TZP and aminoglycosides decreased significantly over the years. On the contrary, the present meta-analysis has revealed that there is an increasing resistance trend in *P. aeruginosa* against TZP in Turkey. This may be attributed to the fact that TZP-was the most preferred antibiotic after carbapenems in Turkey [36].

There are some limitations that should be considered while interpreting the results. First, some of the studies might have been missed, due to limited access to some data including those presented in theses or in-press articles. Second, we did not include studies with <10 cases not to increase the heterogeneity between the studies included. Third, differences between phenotypic methods and genotypic methods should be taken into account, because different methods may result in different reports on the prevalence of IMP-resistant *P. aeruginosa*.

Conclusions

Our meta-analysis results revealed that there is a remarkable increase in resistance rates in *P. aeruginosa* to carbapenems and TZP in Turkey due to frequent use [32, 33]. We should avoid using these antibiotics empirically, while other antibiotics with antipseudomonal activity such asFEP and CAZ should be prioritized in the treatment of these infections. To prevent the emergence and spread of bacterial resistance, strict infection control and rational antibiotic use programs should be established and antibiotic resistance profiles should be monitored closely.

Ethics Committee Approval: Ethics committee approval was waived due to being a meta-analysis.

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – SAI, RAC, EY; Design – SAI, LG, EY; Supervision – SAI, SK, EY; Fundings – SAI, LG, RAC; Materials – SAI, RAC, SK; Data collection and/or processing – SAI, LG, SK; Analysis and/or interpretation – SAI, LG; Literature review – SAI, SK; Writing – SAI, EY, RAC; Critical review – SAI, EY.

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