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Efficacy and safety of outpatient parenteral antibiotic therapy in patients with infective endocarditis: a meta-analysis

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ABSTRACT

Background. To investigate the clinical outcome of patients with infective endocarditis (IE) during and after outpatient parenteral antimicrobial treatment (OPAT), and to further clarify the safety and efficacy of OPAT for IE patients.

Methods. Through December 20, 2021, a total of 331 articles were preliminarily searched in Pubmed, Web of Science, Cochrane Library and Embase, and 9 articles were eventually included in this study.

Results. A total of 9 articles comprising 1,116 patients were included in this study. The overall mortality rate of patients treated with OPAT was 0.04 (95% CI, 0.02-0.07), that means 4 deaths per 100 patients treated with OPAT. Separately, mortality was low during the follow-up period after OPAT treatment, with an effect size (ES) of 0.03 (95%CI, 0.02-0.07) and the mortality of patients during OPAT treatment was 0.04 (95% CI, 0.01-0.12). In addition, the readmission rate was found to be 0.14 (95% CI, 0.09-0.22) during the follow-up and 0.18 (95% CI, 0.08-0.39) during treatment, and 0.16 (95% CI, 0.10-0.24) for patients treated with OPAT in general. Regarding the relapse of IE in patients, our results showed a low overall relapse rate, with an ES of 0.03 (95% CI, 0.01-0.05). In addition, we found that the incidence of adverse events was low, with an ES of 0.26 (95% CI, 0.19-0.33).

Conclusion. In general, the incidence of adverse events and mortality, readmission, and relapse rates in IE patients treated with OPAT are low both during treatment and follow-up period after discharge, indicating that OPAT is safe and effective for IE patients. However, our study did not com-

pare routine hospitalization as a control group, so conclusions should be drawn with caution. In order to obtain more scientific and rigorous conclusions and reduce clinical risks, it is still necessary to conduct more research in this field and improve the patient selection criteria for OPAT treatment, especially for IE patients. Finally, clinical monitoring and follow-up of OPAT-treated patients should be strengthened.

Keywords: outpatient parenteral antimicrobial therapy (OPAT), infective endocarditis (IE), meta-analysis

Eficacia y seguridad del tratamiento antibiótico domiciliario endovenoso en pacientes con endocarditis infecciosa: un metaanálisis

RESUMEN

Introducción. Investigar el resultado clínico de los pacientes con endocarditis infecciosa (EI) durante y después del tratamiento antibiótico domiciliario endovenoso (TADE), y determinar la seguridad y eficacia del TADE para los pacientes con EI.

Métodos. Hasta el 20 de diciembre de 2021, se realizaron búsquedas preliminares en un total de 331 artículos en Pubmed, Web of Science, Cochrane Library y Embase, y finalmente se incluyeron 9 artículos en este estudio.

Resultados. Se incluyeron un total de 9 artículos con 1.116 pacientes. La tasa de mortalidad global de los pacientes tratados con TADE fue de 0,04 (IC95%: 0,02-0,07), lo que significa 4 muertes por cada 100 pacientes tratados con TADE. Por separado, la mortalidad fue baja durante el periodo de seguimiento después del tratamiento con TADE, con un tamaño del efecto (TE) de 0,03 (IC95%: 0,02-0,07) y la mortalidad de los pacientes durante el tratamiento con TADE fue de 0,04 (IC95%: 0,01-0,12). Además, se encontró que la tasa de readmisión fue de 0,14 (IC95%: 0,09-0,22) durante el seguimiento y de 0,18 (IC95%: 0,08-0,39) durante el tratamiento, y de

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0,16 (IC95%: 0,10-0,24) para los pacientes tratados con TADE de forma global. En cuanto a la recaída de la EI en pacientes, nuestros resultados mostraron una baja tasa global de recaída, con un TE de 0,03 (IC95%: 0,01-0,05). Además, se encontró que la incidencia de eventos adversos fue baja, con una TE de 0,26 (IC95%: 0,19-0,33).

Conclusiones. En general, la incidencia de eventos adversos y las tasas de mortalidad, reingreso y recaída en pacientes con EI tratados con TADE son bajas tanto durante el tratamiento como durante el período de seguimiento después del alta, lo que indica que el TADE es seguro y efectivo para los pacientes con EI. Sin embargo, nuestro estudio no comparó la rutina de hospitalización como grupo de control. Todavía es necesario realizar más investigaciones en este campo y mejorar los criterios de selección de pacientes para el TADE, especialmente en los pacientes con EI. Por último, se debe reforzar la monitorización clínica y el seguimiento de los pacientes tratados con TADE.

Palabras clave: tratamiento antibiótico domiciliario endovenoso, endocarditis infecciosa, metanálisis

INTRODUCTION

Infective endocarditis (IE) is a serious infectious disease with significant associated mortality, and morbidity and results in considerable medical burden to patients. The common pathogenic bacteria causing IE include *Staphylococcus* spp (*Staphylococcus aureus* predominates), *Streptococcus* spp and *Enterococcus* spp, and by other less common organisms such as the HACEK Gram-negative bacilli (*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) and fungi (*Candida* spp, *Aspergillus* spp) [1-4]. The annual incidence of IE is 3-7 cases per 100,000 population, and, despite advances in diagnosis and treatment, mortality in IE patients remains high, with a reported mortality rate of 15-20% in hospital and about 40% per year during follow-up [5-7]. Patients with IE may experience serious complications early, including arterial embolism, infectious metastasis to different organs, and the development of acute heart failure, all of which are major causes of death and the most common cause of emergency valve surgery [7]. Treatment of this complex and serious disease is based on the use of appropriate antibiotics, early detection of complications, and cardiac surgery when appropriate [7].

Outpatient parenteral antimicrobial therapy (OPAT) refers to the monitored administration of parenteral antibiotics in non-inpatient or outpatient settings (e.g., clinic, home, office), and besides shortening the duration of hospitalization, a major reason for OPAT use that it is a strategy to conserve antibiotic expenditures [1,8]. OPAT can be used to treat a wide variety of infections, including skin and soft tissue infections, bone and joint infections, endocarditis, gram-positive bacteremia, increasingly, drug-resistant gram-negative infections, and other specific fungal infections (e.g., cryptococcosis, candidiasis), viral infections (e.g., cytomegalovirus), or protozoa infections (e.g., Leishmania) [8]. Numerous previous studies have shown

that OPAT is safe and effective for the treatment of IE [9-17]. A study by Kortajarena *et al.* reported that only 1 in 194 patients diagnosed with IE died during follow-up after medication [9]. In addition, a prospective cohort study by Perica *et al.* found that the mortality of patients in the OPAT group was significantly lower than that in the control group during the follow-up period of one year after discharge [10]. OPAT is commonly used to consolidate antimicrobial therapy after initial hospitalization and, despite its benefits, it may increase clinical risk due to reduced clinical supervision and monitoring [11]. In addition, studies indicate that even with careful patient selection and a multidisciplinary team-driven treatment plan, the use of potentially toxic antimicrobials and the duration of treatment mean that complications, including treatment failure, and readmission of some patients managed through OPAT are inevitable [11].

Considering the therapeutic effect of OPAT on IE patients and the possible increased clinical risk, and no meta-analysis has been found, we conducted this study to explore the clinical outcome of IE patients after OPAT treatment, and further clarify the safety and efficacy of OPAT in IE patients.

MATERIAL AND METHODS

Search strategy. We searched scientific and medical databases Pubmed, Web of Science, Embase and Cochrane Library for relevant literature, and restricted the language to English. Search terms included "OPAT", "outpatient parenteral antimicrobial therapy (OPAT)", "infective endocarditis (IE)". Through December 20, 2021, 331 studies were retrieved. After the initial screening, the full text was further read to select the studies that could be included. 331 studies were obtained in the preliminary retrieval. Among which, 179 were duplicates, 113 were irrelevant or contained no relevant data, 26 were reviews or conference abstracts, 4 were letters or case reports and were excluded, ultimately including a total of 9 articles (Figure 1). The selection of studies was carried out by two researchers. If the studies selected by them were inconsistent, they would check the studies selected by the other side and focus on the discussion to determine the final literature that could be included.

Inclusion and exclusion criteria. Inclusion criteria were as follows: i) P (patients): the subjects were patients diagnosed with IE; ii) I (intervention): outpatient parenteral antimicrobial therapy; iii) O (outcome): readmission for any cause, all-cause mortality, IE relapse, and adverse events during the treatment or follow-up period.

Exclusion criteria were as follows: i) irrelevant to the research direction or without relevant data; ii) reviews or meeting abstracts; iii) duplicate studies; iv) letters or case reports.

Data Extraction. In this study, the data collected included: the name of the first author, year of publication, total number of subjects, number of IE deaths, readmission recurrence, and number of adverse events during OPAT the treatment and follow-up period.

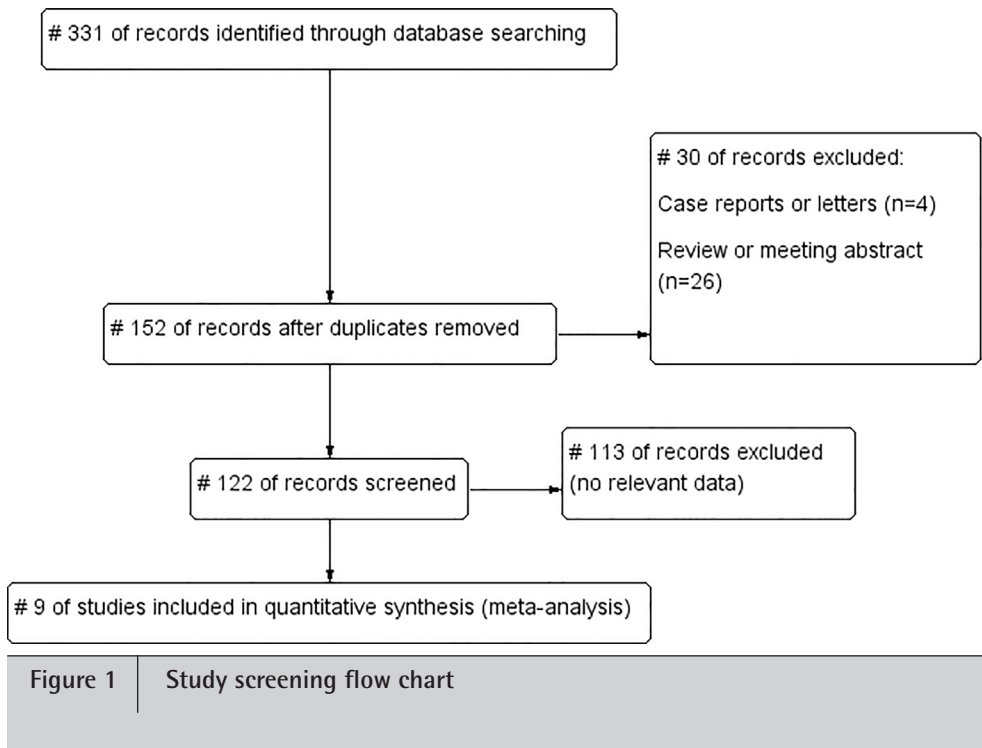


Table 1	Quality assessment of 5 cohort studies								
Study, year [reference]	1	2	3	4	5	6	7	8	Total score
Kortajarena, 2017 [9]	1	1	1	1	2	1	1	1	9
Pericà, 2019 [10]	1	1	1	1	2	1	1	1	9
Htin, 2013 [12]	1	1	1	1	2	1	NA	NA	7
Pajarón, 2017 [13]	1	1	1	1	2	1	NA	NA	7
Cervera, 2011 [15]	1	1	1	1	2	1	1	1	9

1 Selection of the exposed cohort; 2 Selection of the non-exposed cohort; 3 Ascertainment of exposure; 4 Demonstration that outcome of interest was not present at start of study; 5 Comparability of cohorts on the basis of the design or analysis; 6 Assessment of outcome; 7 Was follow-up long enough for outcomes to occur; 8 Adequacy of follow up of cohorts. NA=not available

Quality assessment of included studies.

a) Quality assessment of 5 cohort studies [9,10,12,13,15]:

The Newcastle-Ottawa Scale (NOS) was used to perform quality assessment (Table 1). The results revealed that 3 cohort studies showed 9 points, and 2 cohort studies showed 7 points. The articles by Htin *et al* [12] and Pajarón *et al* [13] did not describe the results during follow-up period.

b) Quality assessment of 4 retrospective analysis studies [11,14,16,17]:

The Joanna Briggs Institute critical capital checklist for students reporting progress data [18] was used to evaluate the

quality of the 4 retrospective analysis studies, the results are shown in Table 2.

Statistical analysis. This study aims to discuss the clinical outcome of IE patients treated with OPAT, further clarify the safety and effectiveness of OPAT for IE patients, and then compare with the previous hospital-based Antibiotic treatment (HBAT). All statistical analyses were performed using the Stata 14.0 software (Stata corporation, College Station, TX, USA) to calculate and analyze the mortality, readmission and relapse rate of IE patients after OPAT treatment. A 95% confidence interval (95% CI) was used to determine the statistical

Table 2 Quality assessment of 4 retrospective analysis studies.

Study, year [reference]	1. Was the sample frame appropriate to address the target population?	2. Were study participants recruited in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and setting described in detail?	5. Was data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Appropriate statistical analysis?	9. Was the response rate adequate?
Durojaiye, 2021 [11]	Y	N	Y	Y	Y	Y	Y	Y	Y
Partridge, 2012 [14]	N	N	N	Y	Y	Y	Y	Y	Y
Lacroix, 2014 [16]	Y	N	N	Y	Y	Y	Y	Y	Y
Amodeo, 2009 [17]	N	N	Y	Y	Y	Y	Y	Y	Y

Y=yes; N=no.

Table 3 The basic information of the included literature.

Study, year [reference]	Study design	Treatment period			Follow up period			Total (n)	Adverse events (n)
		Mortality (n)	Relapse (n)	Readmission (n)	Mortality (n)	Relapse (n)	Readmission (n)		
Kortajarena, 2017 [9]	Cohort Study	-	-	-	1	-	35	194	-
Pericà, 2019 [10]	Cohort Study	-	-	-	33	6	47	429	-
Durojaiye, 2021 [11]	Retrospective analysis	-	-	41	4	8	-	146	-
Htin, 2013 [12]	Cohort study	2	2	3				68	-
Pajarón, 2017 [13]	Cohort study	0	3	6	-	-	-	54	11
Partridge, 2012 [14]	Retrospective analysis	-	-	-	1	1	4	34	12
Cervera, 2011 [15]	Cohort study	-	-	-	3	-	12	73	-
Lacroix, 2014 [16]	Retrospective analysis	1	-	6	-	-	-	18	-
Amodeo, 2009 [17]	Retrospective analysis	-	-	10	2	-	5	100	27

significance of the effect. The results of all studies (effect size (ES) values) were summarized using a random effect model.

RESULTS

Characteristics of the included studies. The characteristics of all the included studies are shown in Table 3. A total of 9 studies comprising 1,116 patients were included in this study, of which 5 described mortality, readmission and recurrence rates during OPAT treatment, and 6 described patient outcomes during follow-up.

Meta-analysis. Two studies showed low mortality during OPAT, with an ES value of 0.04 (95% CI, 0.01–0.12), and 6 studies which including 976 patients showed low mortality during the follow-up period after OPAT, with an ES value of 0.03 (95% CI, 0.02–0.07). The results of these 8 included studies involving 1062 patients showed that the overall mortality of IE patients treated with OPAT was 0.04 (95% CI, 0.02–0.07), $P < 0.01$ (Figure 2A). In addition, 5 studies involving 386 patients was 0.18 (95% CI, 0.08–0.39) during the treatment period, and another 5 studies with 830 patients showed that the readmission rate was 0.14 (95%CI, 0.09–0.22) during the follow-up period,

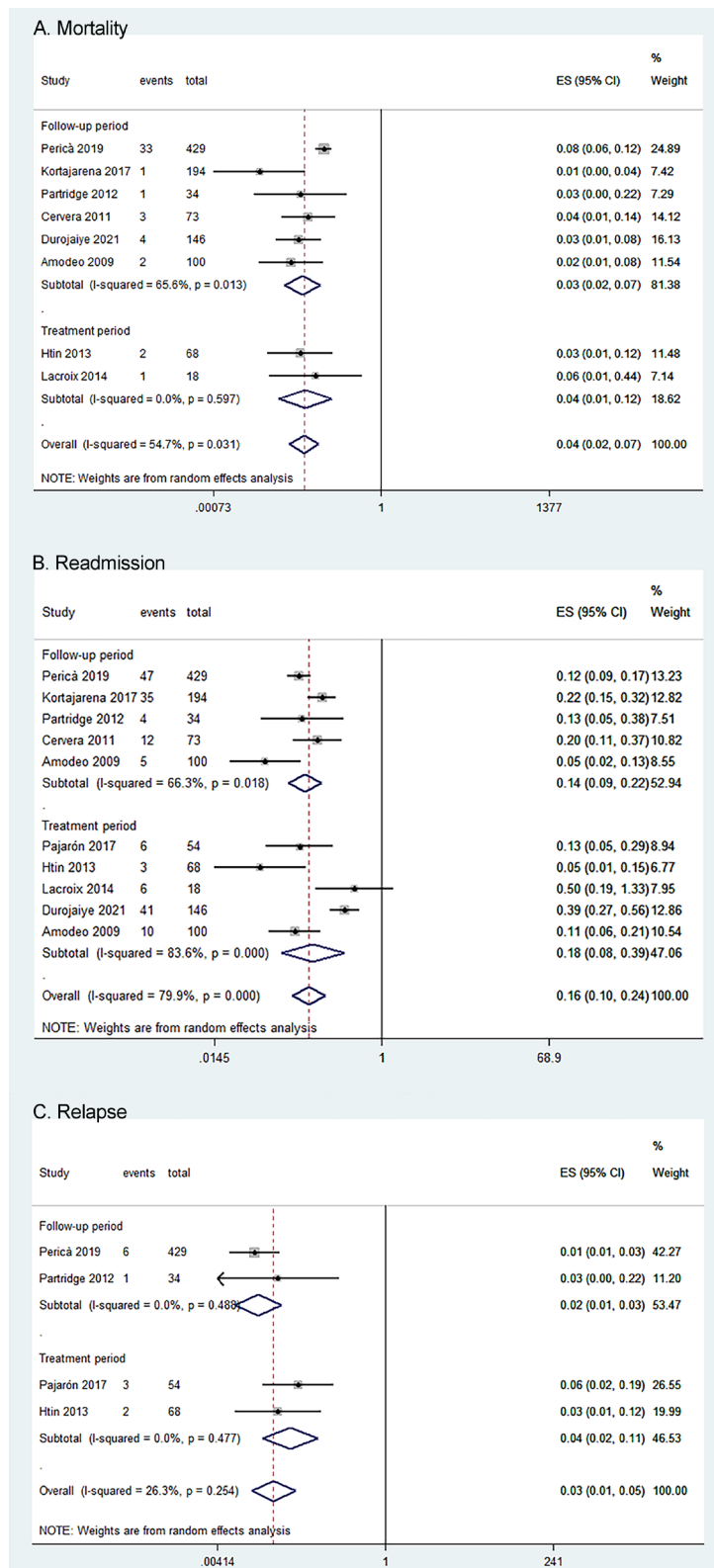


Figure 2 Forest plot of mortality (A), readmission (B), and relapse (C) rates of IE patients treated with OPAT

with an ES value of 0.16 (95% CI, 0.10-0.24) overall (Figure 2B). Regarding the relapse in IE patients, 4 included studies involving 585 patients showed a low overall relapse rate of 0.03 (95%CI, 0.01-0.05), $P < 0.01$ (Figure 2C).

Regarding the incidence of adverse events in IE patients treated with OPAT, 3 included studies which including 188 patients showed that the incidence of adverse events was 0.26 (95%CI, 0.19-0.33), $P < 0.01$ (Figure 3). The available data showed that the incidence of adverse events was low in patients treated with OPAT.

Funnel plot analysis showed that there was no particularly significant publication bias in the included literature (Figure 4).

DISCUSSION

A total of 9 studies were included in this study, and the results revealed that OPAT is generally effective and safe for IE patients. The overall mortality rate for patients treated with OPAT was low, namely 0.04 (95%CI, 0.02-0.07). In addition, the overall readmission and relapse rates of IE patients were low, namely 0.16 (95%CI, 0.10-0.24) and 0.03 (95%CI, 0.01-0.05), respectively. Our results are similar to those of previous studies. A study by Htin *et al.* showed that of 68 patients treated with OPAT, 2 recurred and 2 died, with a one-year survival rate of 96% [12]. Current research data show that OPAT has a good therapeutic effect on IE patients, and it is expected that OPAT will continue to show a good effect in the treatment of IE patients in the future. OPAT has also shown many benefits, such as providing significant cost effectiveness to inpatient management [1,13,16,19,20], not only by reducing the cost of treatment for patients, but also by bringing benefits to the healthcare delivery system. A study from Europe showed that the use of OPAT therapy for IE reduced costs by approximately €15,000 per patient [16]. Also, Goenaga *et al.* noted that OPAT reduced the burden of IE on hospital resources, beds and the limited time of health professionals [21]. In addition, outpatient treatment has been shown to reduce hospital-acquired complications, such as hospital-acquired infections, venous thromboembolism, and stress injuries [8,14,15]. Although OPAT has many benefits, the morbidity and mortality of IE and its limited experience in OPAT treatment mean that the candidate patients are selected carefully. Therefore, the mortality and recurrence rate of OPAT may be much lower than that of patients receiving conventional inpatient treatment. The available results showed that OPAT is relatively safe and effective for IE, however, more studies are needed to compare OPAT with routine hospitalization for IE patients (such as HBAT).

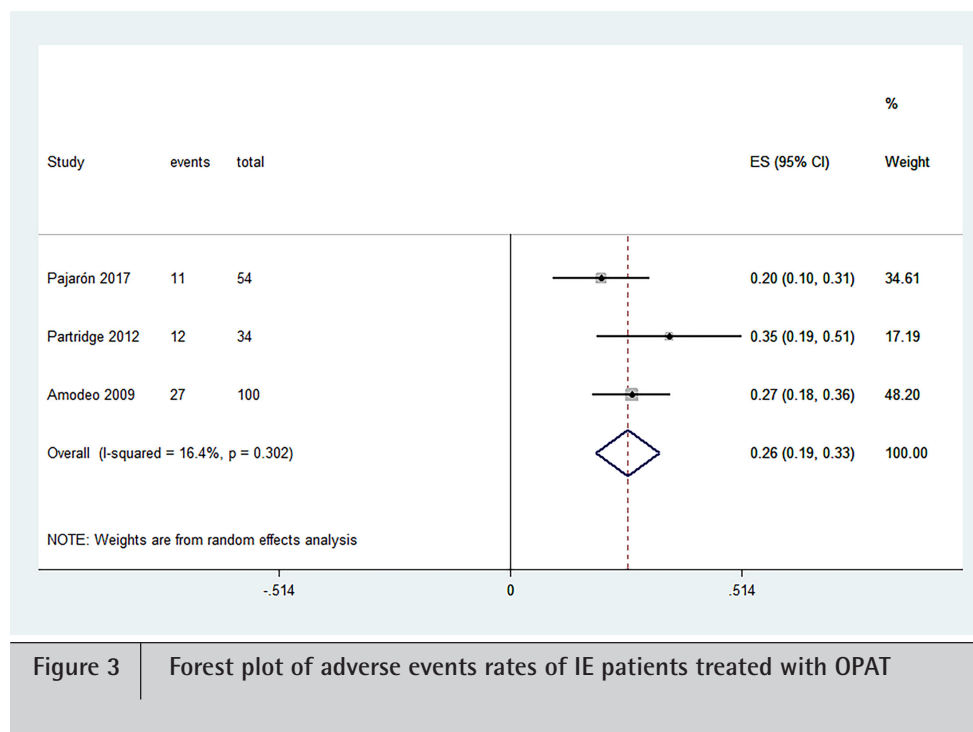


Figure 3 Forest plot of adverse events rates of IE patients treated with OPAT

Most OPATs follow two main models: First, infusion in the patient's home, which is called "health care professional outpatient parenteral antimicrobial therapy (H-OPAT)", with active caregiver intervention. Second, "self-service outpatient parenteral antimicrobial therapy (S-OPAT)", in which health-care personnel initially train patients and/or their caregivers in the use of antimicrobial agents, so the physical presence of healthcare personnel at home during infusion is subsequently unnecessary [13,22]. In the above two modes of OPAT services, the relationship between patients and medical staff is not very close. Although our results showed the effectiveness of OPAT in IE patients and the incidence of adverse events was low, many IE patients still experienced adverse events with an ES value of 0.26 (95%CI, 0.19-0.33). Therefore, it may be necessary to strengthen the monitoring of patients with these two modes of OPAT services. Besides, there is a third type that applies in the case of patients with IE, consisting of a first phase of hospital treatment that gives way to OPAT in a series of very selected patients.

Previous studies have shown that patients treated with OPAT receive less intensive observation than hospitalized patients, and OPAT may increase clinical risk unless there are clear standards and protocols for patient supervision consistent with existing national and international practice guidelines [11,14]. Durojaiye *et al.* found that pre-existing renal failure and comorbidities (Charlson comorbidity index score) were strongly associated with OPAT treatment failure. Also, patients with a prior history of IE and cardiac complications, such as severe valvular insufficiency, perivalvular abscesses, or internal cardiac fistula, were more likely to have poorer long-term out-

comes [11]. Moreover, studies have shown that endocarditis patients with artificial heart valves, consistently positive blood culture results, poorly controlled congestive heart failure, large neoplasms (>10 mm in length), recurrent embolic events, *S. aureus* etiology, or conduction abnormalities are at increased risk for clinical complications, and therefore inpatient treatment or daily outpatient follow-up during the first 2 weeks of treatment is recommended [22-24]. Andrews *et al.* recommended that patients with uncomplicated endocarditis caused by viridans group streptococci be discharged from hospital after 1 week to receive OPAT treatment [24]. Therefore, it is very important to select the right IE patients for OPAT at the right time. Furthermore, it is also necessary to strengthen the monitoring and follow-up of IE patients treated with OPAT, including monitoring the patients' vital signs, complications and relevant laboratory indicators to reduce the occurrence of adverse events. Especially for patients receiving OPAT in the community center or at home, establishing a robust approach to patient monitoring and review is critical [8]. A study has shown that the OPAT Medical Service has established procedures for routine and emergency examination of patients [14]. At Sheffield in the UK, patients are followed up in the OPAT ward at least once a week, this frequent clinical contact facilitates the early detection of complications or clinical deterioration [14], thereby reducing the rate of recurrence and mortality. Finally, it is critical to develop a well-trained OPAT team. Overall, we believe that the benefits of OPAT in the treatment of IE patients outweigh the disadvantages.

This study has some shortcomings. First, we only included English literature, and thus many non-English reports may

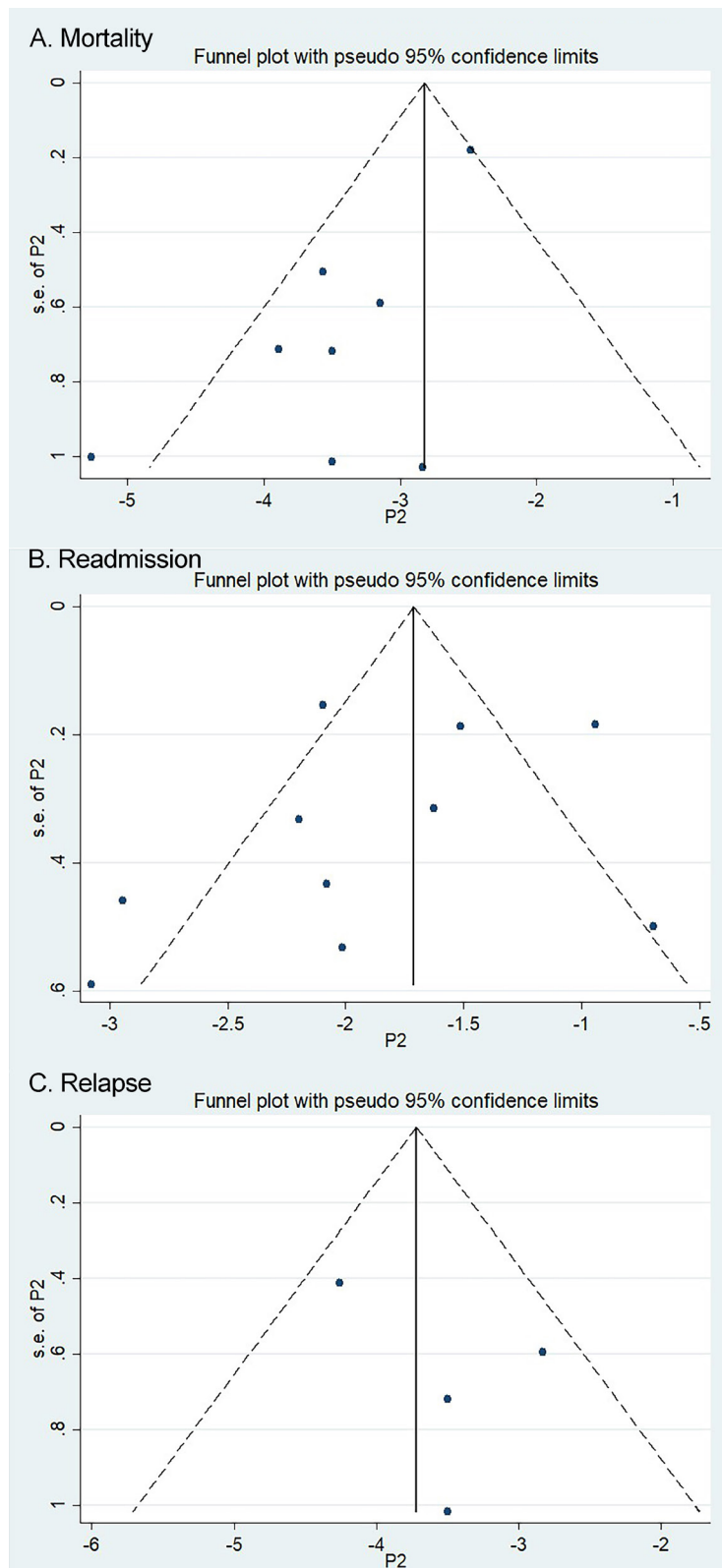


Figure 4 Funnel plot of the included literatures: mortality (A), readmission (B), and relapse (C).

be omitted. Second, there was no specific data on the sex differences, age and underlying diseases of patients in the included studies, so there was no subgroup analysis in this respect, and the influence of these confounding factors on the study results cannot be excluded. Finally, since not all articles included data during OPAT treatment and follow-up after discharge, it was impossible to compare the clinical outcomes during treatment and follow-up. In addition, the data on adverse events of OPAT are too few, and the number of patients included for the variable adverse effects is really low, thus more research data are still needed to confirm the safety of OPAT.

In general, the mortality, readmission, and relapse rates and incidence of adverse events in IE patients treated with OPAT are low both during treatment and follow-up after discharge, indicating that OPAT is safe and effective for IE patients. However, our study did not compare routine hospitalization as a control group, so conclusions should be drawn with caution. In order to obtain more scientific and rigorous conclusions and reduce clinical risks, it is still necessary to expand research in this field and improve the patient selection criteria for OPAT service, especially for IE patients, prudent and selective use of OPAT may produce optimal treatment effects for patients. Finally, clinical monitoring and follow-up of patients treated with OPAT should be strengthened.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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