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ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Assessment of the Reporting Quality of Randomized Controlled Trials on Esketamine Administration for the Treatment of Major Depressive Disorder According to the CONSORT Statement

Αξιολόγηση της Αναφερόμενης Ποιότητας Τυχαιοποιημένων Κλινικών Μελετών που Αφορούν την Χορήγηση Εσκεταμίνης για την Θεραπεία της Μείζονας Καταθλιπτικής Διαταραχής Σύμφωνα με την Δήλωση CONSORT

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Contents

Abstract

Background

Major Depressive Disorder (MDD) is a leading cause of global disability, with Treatment-Resistant Depression (TRD) posing significant challenges for management. Intranasal esketamine offers a novel therapeutic option, yet the reporting quality of randomized controlled trials (RCTs) for its efficacy and safety remains underexplored. High-quality reporting is essential for reliable evidence and decision-making. The CONSORT 2010 statement enhance transparency and completeness in clinical trial reporting.

Objective

To evaluate the reporting quality of RCTs on intranasal esketamine for MDD using the CONSORT 2010 statement.

Methods

A literature search was conducted in MEDLINE/PubMed, Scopus, and Web of Science for RCTs published between 2016 and 2024. Studies were assessed for compliance with the 37-item CONSORT checklist. The primary endpoint was the mean CONSORT adherence. Secondary endpoints included individual item adherence and potential influencing factors. Univariate analysis and correlation test were applied.

Results

Eleven RCTs with 2729 participants were included. Mean CONSORT adherence was 72.43% (SD = 7.03%), with 54.55% achieving ≥75% compliance. High adherence was noted for outcomes and statistical methods (100%), while allocation concealment (0%) and implementation methods (27%) were inadequately reported. Harms reporting was suboptimal (55%). Univariate analysis showed a borderline association between IF and reporting quality ($p=0.08$), with a significant positive correlation ($\rho=0.756$, $p=0.007$).

Discussion

Moderate adherence to CONSORT guidelines was observed, with notable performance in outcomes reporting but significant gaps in allocation concealment and harms reporting. Improved transparency is needed to minimize bias and enhance evidence reliability.

Conclusion

Enhancing adherence to CONSORT statement is vital for improving the reliability of RCT findings and advancing research in treatment-resistant depression.

Keywords Esketamine, Major Depressive Disorder, CONSORT, Reporting Quality, Randomized Controlled Trials, Treatment-Resistant Depression

Περίληψη

Ιστορικό

Η Μείζονα Καταθλιπτική Διαταραχή (ΜΚΔ) αποτελεί κύρια αιτία παγκόσμιας αναπηρίας, με τη ανθεκτική στη θεραπεία κατάθλιψη να θέτει σημαντικές προκλήσεις για τη διαχείριση. Η ενδορινική εσκεταμίνη προσφέρει μια νέα θεραπευτική επιλογή, ωστόσο η ποιότητα αναφοράς των τυχαιοποιημένων κλινικών δοκιμών (RCT) για την αποτελεσματικότητα και την ασφάλειά της παραμένει αδιερεύνητη. Η υποβολή εκθέσεων υψηλής ποιότητας είναι απαραίτητη για την αξιοπιστία των ευρημάτων και τη λήψη τεκμηριωμένων αποφάσεων. Η δήλωση CONSORT 2010 ενισχύει τη διαφάνεια και την πληρότητα στην αναφορά κλινικών δοκιμών.

Στόχος

Η αξιολόγηση της ποιότητας αναφοράς των RCTs για την εσκεταμίνη στη ΜΚΔ σύμφωνα με τη δήλωση CONSORT 2010.

Μέθοδοι

Πραγματοποιήθηκε βιβλιογραφική ανασκόπηση στις βάσεις δεδομένων MEDLINE/PubMed, Scopus και Web of Science για RCTs που δημοσιεύτηκαν από το 2016 έως το 2024. Οι μελέτες αξιολογήθηκαν ως προς τη συμμόρφωση με τη λίστα 37 σημείων της CONSORT. Το πρωταρχικό καταληκτικό σημείο ήταν η μέση συμμόρφωση με τις κατευθυντήριες γραμμές CONSORT. Τα δευτερεύοντα καταληκτικά σημεία περιλάμβαναν τη συμμόρφωση ανά επιμέρους στοιχείο και τους πιθανούς παράγοντες επιρροής. Πραγματοποιήθηκαν μονοπαραγοντική ανάλυση και δοκιμή συσχέτισης.

Αποτελέσματα

Συμπεριλήφθηκαν 11 RCTs με 2729 συμμετέχοντες. Η μέση συμμόρφωση ήταν 72.43% (SD = 7.03%), με το 54.55% να επιτυγχάνει συμμόρφωση ≥75%. Υψηλή συμμόρφωση παρατηρήθηκε στα αποτελέσματα και τις στατιστικές μεθόδους (100%), ενώ η περιγραφή των μηχανισμών που χρησιμοποιήθηκαν για την εφαρμογή και απόκρυψη της τυχαίας ακολουθίας (0%) και η αναφορά στο ποιοι πήραν μέρος στην δημιουργία της τυχαίας ακολουθίας, στην στρατολόγηση των ασθενών αλλά και στην εγγραφή τους σε κάθε παρέμβαση (27%) αναφέρθηκαν ανεπαρκώς. Η αναφορά των ανεπιθύμητων ενεργειών ήταν επίσης χαμηλή (55%). Η μονοπαραγοντική ανάλυση έδειξε οριακή συσχέτιση μεταξύ του IF και της ποιότητας αναφοράς ($p=0.08$), ενώ η συσχέτιση ήταν στατιστικά σημαντική ($\rho=0.756$, $p=0.007$).

Συζήτηση

Η συμμόρφωση με τις κατευθυντήριες γραμμές CONSORT ήταν μέτρια. Απαιτείται βελτίωση της διαφάνειας για την ελαχιστοποίηση της μεροληψίας και την ενίσχυση της αξιοπιστίας των δεδομένων.

Συμπέρασμα

Η ενίσχυση της συμμόρφωσης με τη δήλωση CONSORT είναι ζωτικής σημασίας για τη βελτίωση της αξιοπιστίας των ευρημάτων των RCTs και την προώθηση της έρευνας στην ανθεκτική στη θεραπεία κατάθλιψη.

Λέξεις-κλειδιά Εσκεταμίνη, Μείζονα Καταθλιπτική Διαταραχή, CONSORT, Ποιότητα Αναφοράς, Τυχαιοποιημένες Κλινικές Μελέτες, Ανθεκτική στη Θεραπεία Κατάθλιψη

Introduction

Major depressive disorder (MDD) is a widespread and devastating mental health condition, recognized as one of the leading causes of disability worldwide. Affecting approximately 5.0% of the adult population, MDD plays a significant role in the overall global burden of disease, a contribution that has further increased during the COVID-19 pandemic [1,2]. However, MDD is a heterogenous multifactorial disease with poorly understood pathological and pharmacological mechanisms, and its available diagnostic and treatment options remain inadequate. Despite Selective serotonin reuptake inhibitors (SSRIs) and Serotonin and norepinephrine reuptake inhibitors (SNRIs) are the first-line treatments, a considerable portion of patients fail to achieve an effective response to these treatments [3]. Evidence indicates that nearly 30% of MDD patients fail to achieve remission after multiple therapeutic attempts, leading to treatment-resistant depression (TRD). TRD is commonly defined as failure to respond to two or more adequate medications, although definitions vary, and it is associated with heightened risks of recurrence, suicide, and significant burdens that affect not only individuals but also their social environment, health care providers, and society as a whole. These challenges highlight the urgent need for effective therapeutic options [4-6].

Esketamine, S-enantiomer of ketamine racemate, an N-methyl-D-aspartate receptor antagonist formulated as nasal spray, was approved at first at United States by the U.S. Food and Drug Administration (FDA) and later at Europe by the European Medicines Agency (EMA) for the treatment of adults with TRD and symptoms of depression in individuals with MDD who are facing acute suicidal ideation or behaviors [7,8]. The U.S. FDA submission was supported by efficacy findings from these phase 3 clinical trials (TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3) and one relapse prevention study (SUSTAIN-1). From the three acute phase studies, only TRANSFORM-2 meet the statistical significance at primary endpoint. [9-12]. However, most of the esketamine (ESK) studies demonstrated an approximate 4-point reduction in the Montgomery Asberg Depression Rating Scale (MADRS) in contrast with antidepressant plus placebo nasal spray, exceeding the 2-point threshold typically considered clinically significant [13]. The National Institute for Health and Care Excellence (NICE) has not recommended nasal esketamine for depression due to uncertainties in the available evidence, a stance shared by several authors who have raised concerns about its safety and efficacy [14-17].

Randomized controlled trials (RCTs) represent a critical foundation for evidence-based medicine, providing critical data to inform therapeutic strategies and clinical decision-making. However, the validity of their findings depends on methodological rigor and transparent reporting [18,19]. In the context of antidepressant research, challenges such as unblinding, selective reporting, bias in managing missing data, and placebo response—driven by expectancy effects and intensive trial settings—have raised concerns about the reliability of evidence [20, 21]. These issues highlight the importance of ensuring transparency in trial design and reporting to produce credible and applicable evidence. To address these challenges, the CONSORT (Consolidated Standards of Reporting Trials) Statement was introduced in 1996, with updates in 2001 and 2010, providing a structured 25item-checklist and flow diagram to enhance the quality of RCT reporting [22-24]. The CONSORT guidelines standardize methodological reporting, enabling critical evaluation of findings and supporting evidence-based practice in clinical research.

To the best of our knowledge, no prior study has assessed the reporting quality of RCTs on esketamine nasal spray for depression following the CONSORT guidelines. The most recent study, published in April 2023, evaluated the reporting of adverse events (AEs) in intranasal esketamine trials using the CONSORT extension for harms reporting in randomized trials [25].

The presents study aims to evaluate the reporting quality of RCTs on esketamine in depression, published from 2016 to 2024, using the CONSORT 2010 guidelines.

Methods

Literature Search

An electronic structured literature search was performed using MEDLINE/PubMed, Scopus and Web of Science databases to identify relevant randomized controlled trials (RCTs) on esketamine for depression. The search algorithm combined the terms [(esketamine OR S-ketamine) AND (depression OR major depressive disorder OR depressive disorder)] in all fields. The search was restricted to studies classified as "Randomized Controlled Trial," involving humans, and published in English. Articles published between January 1, 2016, and December 31, 2024, were included. Titles and abstracts of the retrieved articles were carefully examined for eligibility, and full texts were accessed when initial screening did not provide sufficient information for determination.

Eligibility of studies

Inclusion criteria:

- Published between January 1, 2016 until December 31, 2024
- Identified as randomized trials with a parallel group design, where human participants were prospectively assigned to two or more intervention groups
- Adult patients diagnosed with MDD
- At least one intervention arm using esketamine nasal spray combined with standard care irrespective of the comparator (placebo or active)
- Published in English

Exclusion criteria:

- Pilot studies
- Other study designs such as crossover RCTs, quasi-randomized and non-randomized studies
- Study protocols
- Conference abstracts
- Sub-group and post-hoc analysis of published trials
- Studies investigating esketamine administration via non-nasal routes (e.g., oral or intravenous)
- Studies involving racemic ketamine or ketamine mixtures

Reporting assessment tool

The updated guidelines outlined in the 2010 CONSORT Statement were applied, comprising a questionnaire of 25 items, with 12 of them divided into two parts, resulting in a total of 37 items [24]. The evaluation of RCTs was systematically guided by the CONSORT elaboration and explanation statement, which comprehensively addresses all aspects of a clinical trial, including title, abstract, introduction, methods, results, discussion, and other information.

Data extraction

All eligible articles were evaluated one by one according to the CONSORT Statement and each of the 37 items was appraised equally by 1 point for proper reporting and by 0 for insufficient, inconsistent, or missing information. Except for the "other information" category (independent of the section) and item 14a (dates defining the recruitment and follow-up, which may appear

in either the Methods or Results sections), any item reported elsewhere of its designated CONSORT section (title, abstract, introduction, methods, results, or discussion) would be zero rated. Informations explained in supplementary appendices were considered valid only if they were cited in the main text. However, item 8a was an exception to this rule, as outlined in the CONSORT guidelines, and was scored by 1 if it was included in the main body of the article. For the three items with statements “When applicable” (7b), “If done” (11a), or “If relevant” (11b), they were marked as “non-applicable” if the response was a clear yes or no; then the response of these was analyzed accordingly. The assessment produced a final score ranging from 0 to 37.

Further data collected included the publication year, journal ranking [5-year Impact Factor (IF) reported in 2023 by Clarivate Analytics via Journal Citation Reports], the authors number, the sample size, and the citation count.

Outcome measures and Statistical analysis

The primary endpoint was the mean CONSORT adherence of the eligible RCTs. Compliance exceeding 75% with the CONSORT items was considered the threshold. Secondary, adherance of each item individually and potential determining factors were also evaluated. Descriptive statistics were applied to evaluate the CONSORT adherence of the retrieved trials. The factors were considered as nominal variables, IF (classified as low <5.2 and high ≥5.2 based on the median), sample size (<227 patients randomized ≥227 patients randomized based on the median), citations (<184 ≥184 based on the median) and number of authors (≤11 authors >11 authors based on the median of the sample). All parameters, were analyzed univariately with Pearson’s chi-squared test (or Fisher’s exact test for small observed counts). Multivariate analysis was conducted using binary logistic regression to identify potential associations with reporting quality. An arbitrary p-value threshold of 0.20 was set as the cut-off for variables to enter the binary logistic regression, while stricter p-value of 0.05 was used to determine significance in the multivariate analysis. Results are reported, including odds ratios (ORs), 95% confidence intervals (CIs), and p-values. Addition analysis was conducted to explore a potential correlation between IF and CONSORT adherence. SPSS Statistics Software Version 28 was used.

Ethical view

Ethical approval was not necessary for this study, as it relied exclusively on publicly accessible data from existing RCT reports and did not involve human participants.

Results

A total of 693 studies were initially retrieved from databases extraction. After eliminating duplicate entries, 477 records remained. Screening of titles and abstracts resulted in the identification of 51 potentially relevant articles. Following a detailed full-text review, 11 studies were included in the final analysis. The search process, summarized in five distinct steps, is presented in the flow diagram (Figure 1).

CONSORT adherence

According to the evaluation of the studies, the mean adherence to the CONSORT guidelines was 72.43% (SD = 7.03%, Median = 75.00) with minimum and maximum compliance rates of 58.33% and 80.56% respectively. Six of the studies (54.55%) demonstrated good reporting quality (≥75% compliance) while five (45.45%) had lower adherence, reporting less than 75% of the CONSORT items. The average compliance rate for each study is shown in Table 1 and Figure 2.

Adherence per CONSORT item was calculated and is presented in Table 2 and Figure 3. Notably, 11 out of the 37 checklist items (29.73%) were fully reported in all (100%) of the included studies while 22 items (59.5%) were reported across 75% or more of the studies. Among these, the title/abstract and introduction section exhibited the highest compliance, with 3 out of four items (75%) reported in over 75% of studies. Conversely, the results section showed the lowest adherence, with only 5 out of 10 items (50%) meeting this threshold, followed by the methods section, which included 10 out of 17 items (58.8%) at this level of compliance.

Despite the high adherence observed for critical CONSORT items such as pre-specified outcomes (item 6a, 100%), statistical methods (item 12a, 100%), random allocation sequence generation (item 8a, 91%), and primary and secondary outcomes reporting (item 17a, 91%), significant shortcomings were noted. In particular, no study reported the mechanism used to implement the random allocation sequence (item 9, 0%), while low compliance was observed

for identifying those responsible for sequence generation and assignment (item 10, 27%) and presenting effect sizes for binary outcomes (item 17b, 45%).

Determinants of reporting quality

To investigate potential factors associated with overall reporting quality (CONSORT compliance), univariate analysis was conducted based on categorized variables (IF ≥5.2, sample size ≥227, citations ≥184, and number of authors >11). As summarized in Table 3, the journal's impact factor (IF) emerged as the only parameter nearing statistical significance, with OR=13.45 (95% CI: 0.601–1160.387, p=0.08). Although it did not reach the conventional $p<0.05$ threshold, the p-value of 0.08 suggests a borderline association that warrants further consideration. Conversely, sample size (OR=2.70, p=0.57), number of citations (OR=2.70, p=0.57), and number of authors (OR=1.45, p=1.00) showed no meaningful association with reporting quality in this analysis. Given the lack of statistically significant associations in the univariate analysis, no variables were deemed robust predictors to proceed with multivariate logistic regression modeling.

An additional analysis (Fig. 4) was conducted to investigate the correlation between journal impact factor (5-year IF) and overall reporting quality (CONSORT compliance). The results revealed a strong positive correlation between the two variables (Spearman's $\rho=0.756$, p=0.007), which was statistically significant ($p<0.01$). These findings suggest that articles published in journals with higher impact factors tend to exhibit better reporting quality based on CONSORT criteria.

Discussion

The present study evaluated the reporting quality of randomized controlled trials (RCTs) on intranasal esketamine for depression, based on the CONSORT 2010 Statement. Among the 11 studies analyzed, which included a total of 2729 randomized participants, the general adherence to CONSORT guidelines was moderate, with an average compliance rate of 72.43%. Despite the limited number of trials, the participant count is notable and compares favorably to the typically smaller sample sizes seen in ketamine studies [33]. Moreover, six of these trials, representing more than half, achieved a compliance rate above 75%, while a majority of the items (59.5%) were sufficiently reported.

Reporting of key methodological features was suboptimal, particularly regarding randomization and blinding. Notably, the allocation concealment mechanism, which includes steps to conceal the randomized sequence until assignment, was entirely unreported across all studies (0%). Furthermore, the identification of individuals responsible for sequence generation and assignment was insufficient, with compliance observed in only 27% of the studies. Additionally, only 55% of the studies provided details on who was blinded after the assignment and how. While the type of randomization (91%) and the similarity of interventions (82%) were generally well explained, these omissions in randomization and blinding practices raise concerns about potential biases. Given their importance in establishing the internal validity of a study, greater emphasis on allocation concealment and blinding in future trials is crucial [34]. Items addressing the study design, the primary pre-specified outcomes, and the statistical analysis plan were well-reported, demonstrating strong adherence to CONSORT guidelines in these critical aspects.

Adherence to items in the results section varied across different aspects. It is worth to mention that the inclusion of a participant flow chart, strongly recommended by the CONSORT statement, was observed in all studies, with eight presenting it in the main article and three in the supplementary materials. Reporting of the number of participants randomized, treated, and analyzed for the primary outcome was relatively high, with compliance reaching 82%. Similarly, losses and exclusions after randomization, along with the corresponding reasons, were adequately reported in 73% of the studies. Outcomes were frequently reported with effect sizes and precision, with a high compliance rate of 91%. Such adherence to key items reinforces the methodological transparency and credibility of the trials, enhancing the reliability and interpretability of their findings. However, the reporting of binary outcomes (45%) and the results of additional and subgroup analysis (55%), was low. A recent systematic review and meta-analysis by Oraee et al. (2024) highlighted discrepancies between full-text presented outcomes and study protocols, identifying these studies as high risk for selective outcome reporting [35]. Reporting of harms was similarly suboptimal, with only 55% compliance observed in the included studies. This finding aligns with previous evaluations in the literature. Taillefer De Laportalière et al. (2023) highlighted that the quality of adverse event reporting in clinical trials evaluating esketamine was low, with inconsistencies in the number of adverse events reported in journal publications [25]. Furthermore, a meta-analysis on reporting bias in trials of second-generation antidepressants revealed that serious adverse events (SAEs) were poorly reported, with over half of the articles failing to address them, and discrepancies between

FDA reviews and publications often presenting a more favorable drug-placebo comparison [36].

Adherence to objective items such as the title, funding, and trial registration was notably consistent across studies, reflecting a strong commitment to transparency in these areas. Protocol availability, however, was less frequently reported, with compliance observed in only 45% of the studies. In contrast, subjective items within the discussion section, such as the interpretation of findings and addressing trial limitations, exhibited moderate adherence.

Compared to previous studies, these findings highlight areas of progress and persistent deficiencies. For instance, the high compliance with outcomes-related items aligns with prior evaluations of reporting quality in other therapeutic areas. However, the lack of adherence to allocation concealment mechanisms remains a recurring issue, as noted in prior assessments of RCTs [37-39].

The univariate analysis explored potential factors associated with CONSORT compliance. Among the variables examined, the journal impact factor (IF) showed a borderline association with reporting quality ($p=0.08$), and an additional analysis revealed a statistically significant positive correlation between IF and CONSORT compliance (Spearman's $\rho=0.756$, $p=0.007$). In contrast, no meaningful associations were observed for sample size, number of citations, or number of authors. However, the small number of included studies may have limited the statistical power of our analysis, potentially hindering the detection of significant relationships.

This study has several limitations that should be acknowledged. First, the number of RCTs included in the analysis was relatively small, which may have hindered the detection of statistically significant associations in certain analyses. Furthermore, the inclusion criteria were restricted to studies published in English, potentially omitting relevant research published in other languages.

The fact that all the analyzed studies were funded by the same pharmaceutical company raises concerns about potential bias in reporting and framing of results. Previous studies have demonstrated that industry-funded trials are more likely to report favorable outcomes compared to those funded by independent sources [40]. While this does not inherently undermine the validity of the findings, it highlights the need for further research from independent sources to confirm the reported outcomes.

Furthermore, the researcher conducting the evaluation was not blinded to author and journal information, which could introduce subjectivity into the assessment process. Although every

effort was made to apply the CONSORT checklist objectively, this lack of blinding might influence the interpretation of certain items.

Finally, the CONSORT items were assessed as equally weighted, despite some—such as randomization, blinding, and the inclusion of a flow diagram—being of greater importance in ensuring methodological rigor and transparency. This approach may limit the nuanced understanding of reporting quality across studies.

Adherence to the CONSORT statement plays a pivotal role in enhancing the transparency, reliability, and interpretability of randomized controlled trials. By standardizing the reporting of essential methodological and outcome-related details, the CONSORT guidelines enable a more accurate assessment of trial quality and support evidence-based medical decision-making. Encouraging adherence to these guidelines is essential not only for researchers, to ensure the clarity and rigor of their work, but also for editors, to uphold standards of transparency and reliability during the publication process, and for readers, to facilitate critical appraisal and informed application of study findings.

Conclusion

To our knowledge, this study is the first to evaluate the reporting quality of RCTs for intranasal esketamine in patients with depression using the CONSORT 2010 guidelines. While overall compliance was moderate, significant areas for improvement remain, particularly regarding randomization and blinding. Strengthening adherence to CONSORT standards is essential for improving the reliability of trial findings and advancing clinical research in this field.

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References

[1] World Health Organization Media Centre: Depression (fact sheet). March 31, 2023. Retrieved from https://www.who.int/news-room/fact-sheets/detail/depression?utm_source=chatgpt.com

[2] Santomauro, D. F., Mantilla Herrera, A. M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D. M., Abbafati, C., Adolph, C., Amlag, J. O., Aravkin, A. Y., … Ferrari, A. J. (2021). Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet, 398*(10312), 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7

[3] Cui, L., Li, S., Wang, S., Wu, X., Liu, Y., Yu, W., Wang, Y., Tang, Y., Xia, M., & Li, B. (2024). Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal transduction and targeted therapy, 9*(1), 30. https://doi.org/10.1038/s41392-024-01738-y

[4] McIntyre, R. S., Alsuwaidan, M., Baune, B. T., Berk, M., Demyttenaere, K., Goldberg, J.F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S., … Maj, M. (2023). Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry, 22*(3), 394–412. https://doi.org/10.1002/wps.21120

[5] Miola, A., Meda, N., Perini, G., & Sambataro, F. (2023). Structural and functional features of treatment-resistant depression: a systematic review and exploratory coordinate-based meta-analysis of neuroimaging studies. *Psychiatry and Clinical Neurosciences, 77*(5), 252–263. https://doi.org/10.1111/pcn.13530

[6] Johnston, K., Powell, L. C., Anderson, I. M., Szabo, S., & Cline, S. (2018). The burden of treatment-resistant depression: a systematic review of the economic and quality of life literature. *Journal of Affective Disorders, 242,* 195-210. https://doi.org/10.1016/j.jad.2018.06.045

[7] US Food and Drug Administration (FDA). March 05, 2019. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified

[8] European Medical Agency (EMA). October 18, 2019. Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 14-17 October 2019. Retrieved from https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-14-17-october-2019

[9] Fedgchin, M., Trivedi, M., Daly, E. J., Melkote, R., Lane, R., Lim, P., Vitagliano, D., Blier, P., Fava, M., Liebowitz, M., Ravindran, A., Gaillard, R., Ameele, H. V. D., Preskorn, S., Manji, H., Hough, D., Drevets, W. C., & Singh, J. B. (2019). Efficacy and Safety of Fixed-Dose

Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *The international journal of neuropsychopharmacology, 22*(10), 616–630. https://doi.org/10.1093/ijnp/pyz039

[10] Popova, V., Daly, E. J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M. E., Shelton, R. C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., Drevets, W. C., & Singh, J. B. (2019). Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *The American journal of psychiatry, 176*(6), 428–438. https://doi.org/10.1176/appi.ajp.2019.19020172

[11] Ochs-Ross, R., Daly, E. J., Zhang, Y., Lane, R., Lim, P., Morrison, R. L., Hough, D., Manji, H., Drevets, W. C., Sanacora, G., Steffens, D. C., Adler, C., McShane, R., Gaillard, R., Wilkinson, S. T., & Singh, J. B. (2020). Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression-TRANSFORM-3. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry, 28*(2), 121–141. https://doi.org/10.1016/j.jagp.2019.10.008

[12] Daly, E. J., Trivedi, M. H., Janik, A., Li, H., Zhang, Y., Li, X., Lane, R., Lim, P., Duca, A. R., Hough, D., Thase, M. E., Zajecka, J., Winokur, A., Divacka, I., Fagiolini, A., Cubala, W. J., Bitter, I., Blier, P., Shelton, R. C., Molero, P., … Singh, J. B. (2019). Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA psychiatry, 76*(9), 893–903. https://doi.org/10.1001/jamapsychiatry.2019.1189

[13] Price, M. Z., & Price, R. L. (2024). Benefits and risks of esketamine nasal spray continuation in treatment-resistant depression. *Biomarkers in Neuropsychiatry*, 11. https://doi.org/10.1016/j.bionps.2024.100104

[14] National Institute for Health and Care Excellence (NICE). (2022 December 14). Esketamine nasal spray for treatment-resistant depression. Retrieved from https://www.nice.org.uk/guidance/ta854. Accessed 12 October 2024.

[15] Gastaldon, C., Papola, D., Ostuzzi, G., & Barbui, C. (2020). Esketamine for treatment resistant depression: a trick of smoke and mirrors? *Epidemiology and Psychiatric Sciences, 29*, e79. https://doi.org/10.1017/S2045796019000751

[16] Cristea, I. A., & Naudet, F. (2019). US Food and Drug Administration approval of esketamine and brexanolone. *The Lancet. Psychiatry, 6*(12), 975–977. https://doi.org/10.1016/S2215-0366(19)30292-5

[17] Turner E. H. (2019). Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval. *The Lancet. Psychiatry, 6*(12), 977–979. https://doi.org/10.1016/S2215-0366(19)30394-3

[18] Slade, M. & Priebe, S. (2001). Are randomised controlled trials the only gold that glitters? *British Journal of Psychiatry, 179*(4), 286–287. https://doi.org/10.1192/bjp.179.4.286

[19] McErlean, M., Samways, J., Godolphin, P.J., & Chen, Y. (2023). The reporting standards of randomised controlled trials in leading medical journals between 2019 and 2020: a systematic review. *Irish Journal of Medical Science, 192*(1), 73–80. https://doi.org/10.1007/s11845-022-02955-6

[20] Moncrieff J. (2001). Are antidepressants overrated? A review of methodological problems in antidepressant trials. *The Journal of nervous and mental disease, 189*(5), 288–295. https://doi.org/10.1097/00005053-200105000-00003

[21] Wang, S.-M., Han, C., Lee, S.-J., Jun, T.-Y., Patkar, A. A., Masand, P. S., & Pae, C.-U. (2017). Efficacy of antidepressants: bias in randomized clinical trials and related issues. *Expert Review of Clinical Pharmacology, 11*(1), 15–25. https://doi.org/10.1080/17512433.2017.1377

[22] Begg, C. (1996). Improving the quality of reporting of randomized controlled trials. *JAMA, 276*(8), 637. https://doi.org/10.1001/jama.276.8.637

[23] Moher, D. (2001). The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials. *JAMA*, 285(15), 1987. https://doi.org/10.1001/jama.285.15.1987

[24] Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M., & Altman, D. G. (2012). CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery, 10*(1), 28–55. https://doi.org/10.1016/j.ijsu.2011.10.001

[25] Taillefer de Laportalière, T., Jullien, A., Yrondi, A., Cestac, P., & Montastruc, F. (2023). Reporting of harms in clinical trials of esketamine in depression: a systematic review. *Psychological medicine, 53*(10), 4305–4315. https://doi.org/10.1017/S0033291723001058

[26] Daly, E. J., Singh, J. B., Fedgchin, M., Cooper, K., Lim, P., Shelton, R. C., Thase, M. E., Winokur, A., Van Nueten, L., Manji, H., & Drevets, W. C. (2018). Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA psychiatry, 75*(2), 139–148. https://doi.org/10.1001/jamapsychiatry.2017.3739

[27] Canuso, C. M., Singh, J. B., Fedgchin, M., Alphs, L., Lane, R., Lim, P., Pinter, C., Hough, D., Sanacora, G., Manji, H., & Drevets, W. C. (2018). Efficacy and Safety of Intranasal Esketamine

for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. *The American journal of psychiatry, 175*(7), 620–630. https://doi.org/10.1176/appi.ajp.2018.17060720

[28] Fu, D. J., Ionescu, D. F., Li, X., Lane, R., Lim, P., Sanacora, G., Hough, D., Manji, H., Drevets, W. C., & Canuso, C. M. (2020). Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *The Journal of clinical psychiatry, 81*(3), 19m13191. https://doi.org/10.4088/JCP.19m13191

[29] Ionescu, D. F., Fu, D. J., Qiu, X., Lane, R., Lim, P., Kasper, S., Hough, D., Drevets, W. C., Manji, H., & Canuso, C. M. (2021). Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *The international journal of neuropsychopharmacology, 24*(1), 22–31. https://doi.org/10.1093/ijnp/pyaa068

[30] Takahashi, N., Yamada, A., Shiraishi, A., Shimizu, H., Goto, R., & Tominaga, Y. (2021). Efficacy and safety of fixed doses of intranasal Esketamine as an add-on therapy to Oral antidepressants in Japanese patients with treatment-resistant depression: a phase 2b randomized clinical study. *BMC psychiatry, 21*(1), 526. https://doi.org/10.1186/s12888-021-03538-y

[31] Reif, A., Bitter, I., Buyze, J., Cebulla, K., Frey, R., Fu, D. J., Ito, T., Kambarov, Y., Llorca, P. M., Oliveira-Maia, A. J., Messer, T., Mulhern-Haughey, S., Rive, B., von Holt, C., Young, A. H., Godinov, Y., & ESCAPE-TRD Investigators (2023). Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. *The New England journal of medicine, 389*(14), 1298–1309. https://doi.org/10.1056/NEJMoa2304145

[32] Chen, X., Hou, X., Bai, D., Lane, R., Zhang, C., Canuso, C., Wang, G., & Fu, D. J. (2023). Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Plus a Newly Initiated Oral Antidepressant in Adult Patients with Treatment-Resistant Depression: A Randomized, Double-Blind, Multicenter, Active-Controlled Study Conducted in China and USA. *Neuropsychiatric disease and treatment, 19*, 693–707. https://doi.org/10.2147/NDT.S391096

[33] Brendle, M., Ragnhildstveit, A., Slayton, M., Smart, L., Cunningham, S., Zimmerman, M. H., Seli, P., Gaffrey, M. S., Averill, L. A., & Robison, R. (2023). Registered clinical trials investigating ketamine and esketamine for treatment-resistant depression: A systematic review. J*ournal of Psychedelic Studies, 6*(3), 176-187. https://doi.org/10.1556/2054.2022.00234

[34] Balshem, H., Helfand, M., Schünemann, H. J., Oxman, A. D., Kunz, R., Brozek, J., Vist, G. E., Falck-Ytter, Y., Meerpohl, J., Norris, S., & Guyatt, G. H. (2011). GRADE guidelines: 3.

Rating the quality of evidence. *Journal of Clinical Epidemiology, 64*(4), 401–406. https://doi.org/10.1016/j.jclinepi.2010.07

[35] Oraee, S., Alinejadfard, M., Golsorkh, H., Sadeghian, M., Fanaei, M., Centis, R., D'Ambrosio, L., Sotgiu, G., Goudarzi, H., Migliori, G. B., & Nasiri, M. J. (2024). Intranasal esketamine for patients with major depressive disorder: A systematic review and meta-analysis. *Journal of psychiatric research, 180*, 371–379. https://doi.org/10.1016/j.jpsychires.2024.11.010

[36] De Vries, Y. A., Roest, A. M., Beijers, L., Turner, E. H., & de Jonge, P. (2016). Bias in the reporting of harms in clinical trials of second-generation antidepressants for depression and anxiety: A meta-analysis. *European Neuropsychopharmacology, 26*(11), 1752–1759. https://doi.org/10.1016/j.euroneuro.2016.09.370

[37] Liampas, I., Chlinos, A., Siokas, V., Brotis, A., & Dardiotis, E. (2019). Assessment of the reporting quality of RCTs for novel oral anticoagulants in venous thromboembolic disease based on the CONSORT statement. *Journal of Thrombosis and Thrombolysis, 48*(4), 542-553. https://doi.org/10.1007/s11239-019-01931-9

[38] Kodounis, M., Liampas, I. N., Constantinidis, T. S., Siokas, V., Mentis, A.-F. A., Aloizou, A.-M., Xiromerisiou, G., Zintzaras, E., Hadjigeorgiou, G. M., & Dardiotis, E. (2020). Assessment of the reporting quality of double-blind RCTs for ischemic stroke based on the CONSORT statement. *Journal of the Neurological Sciences, 15*(415). https://doi.org/10.1016/j.jns.2020.116938

[39] Vrysis, C., Beneki, E., Zintzaras, E., & Doxani, C. (2023). Assessment of the reporting quality of randomised controlled trials for vitamin D supplementation in autoimmune thyroid disorders based on the CONSORT statement. *Endocrine, 80*(2), 346–354. https://doi.org/10.1007/s12020-022-03270-x

[40] Waqas, A., Baig, A. A., Khalid, M. A., Aedma, K. K., & Naveed, S. (2019). Conflicts of interest and outcomes of clinical trials of antidepressants: An 18-year retrospective study. *Journal of psychiatric research, 116*, 83–87. https://doi.org/10.1016/j.jpsychires.2019.05.029

List of Tables and Figures

Table 1.

List of Randomized Control Trials along with the CONSORT (Consolidated Standards of Reporting Trials) score

Article	Medical Journal	Year	Mean Compliance score (%)
Daly et al. [26]	JAMA Psychiatry	2018	75.00
Canuso et al. [27]	American Journal of Psychiatry	2018	80.56
Popova et al. [10]	American Journal of Psychiatry	2019	77.78
Fedgchin et al. [9]	International Journal of Neuropsychopharmacology	2019	70.27
Daly et al. [12]	JAMA Psychiatry	2019	75.68
Fu et al. [28]	Journal of Clinical Psychiatry	2020	63.89
Ochs-Ross et al. [11]	American Journal of Geriatric Psychiatry	2020	72.97
Ionescu et al. [29]	International Journal of Neuropsychopharmacology	2021	75.00
Takahashi et al. [30]	BMC Psychiatry	2021	58.33
Reif et al. [31]	New England Journal of Medicine	2023	80.56
Chen et al. [32]	Neuropsychiatric Disease and Treatment	2023	66.67

Table 2.

Adherence per CONSORT (Consolidated Standards of Reporting Trials) item

	Item No	Checklist item	Compliance (%)
Title and abstract	1a	Identification as a randomized trial in the title	82
	1b	Structured summary of trial design, methods, results, and conclusions	64
Introduction	2a	Scientific background and explanation of the rationale	100
	2b	Specific objectives or hypotheses	100
Methods	3a	Description of trial design (such as parallel, factorial) including allocation ratio	100
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	18
	4a	Eligibility criteria for participants	91
	4b	Settings and locations where the data were collected	82
	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	82
	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	100
	6b	Any changes to trial outcomes after the trial commenced, with reasons	0
	7a	How sample size was determined?	100
	7b	When applicable, explanation of any interim analyses and stopping guidelines	27
	8a	The method used to generate the random allocation sequence	100
	8b	Type of randomization; details of any restriction (such as blocking and block size)	91
	9	The mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	0
	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	27

	11a	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes) and how	55
	11b	If relevant, description of the similarity of interventions	82
	12a	Statistical methods used to compare groups for primary and secondary outcomes	100
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	55
Results	13a	For each group, the numbers of participants who were randomly assigned received intended treatment and were analyzed for the primary outcome	82
	13b	For each group, losses and exclusions after randomization, together with reasons	73
	14a	Dates defining the periods of recruitment and follow-up	100
	14b	Why the trial ended or was stopped	0
	15	A table showing the baseline demographic and clinical	100
	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	100
	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	91
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	45
	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	55
	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	55
Discussion	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, the multiplicity of analyses	73
	21	Generalizability (external validity, applicability) of the trial findings	82
	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	82
Other information	23	Registration number and name of trial registry	91
	24	Where the full trial protocol can be accessed, if available	45
	25	Sources of funding and other support (such as the supply of drugs), the role of funders	100

Table 3.

Univariate analysis of possible determinants of reporting quality

Parameter	OR	95% CI	P value
IF of journal (≥5.2 = median)	13.45	0.601-1160.387	0.08
Sample Size (≥227 = median)	2.70	0.155-63.776	0.57
Citations (≥184 = median)	2.70	0.155-65.776	0.57
Number of authors (>11 = median)	1.45	0.082-30.80	1.00

Figure 1.

Flow diagram of Literature Search

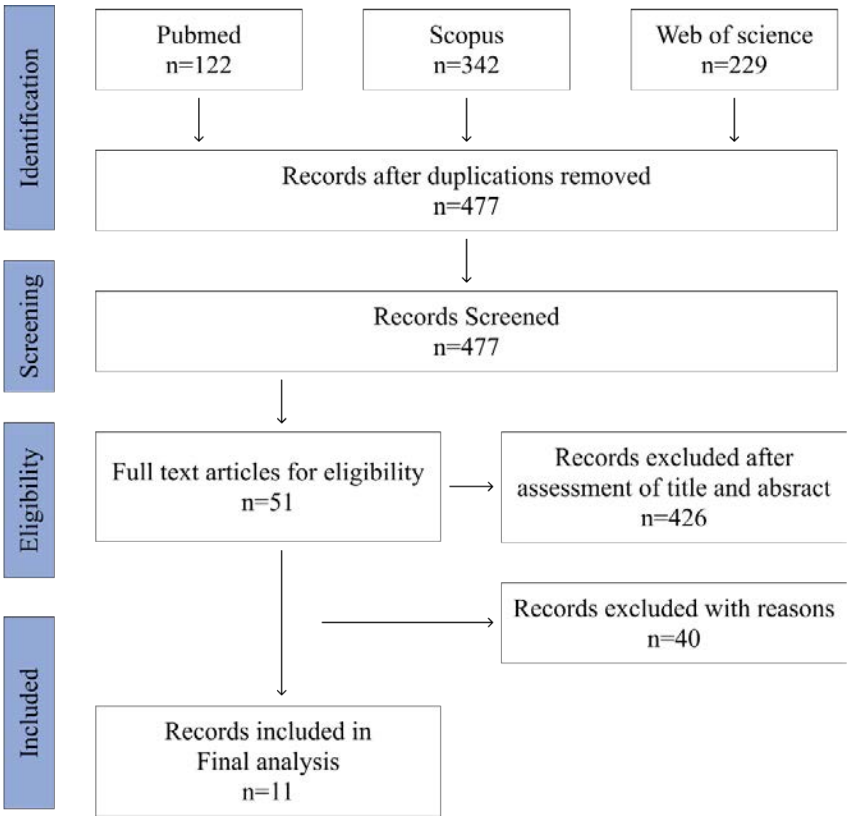

Figure 2.

Distribution of the Total CONSORT scores of the 11 items

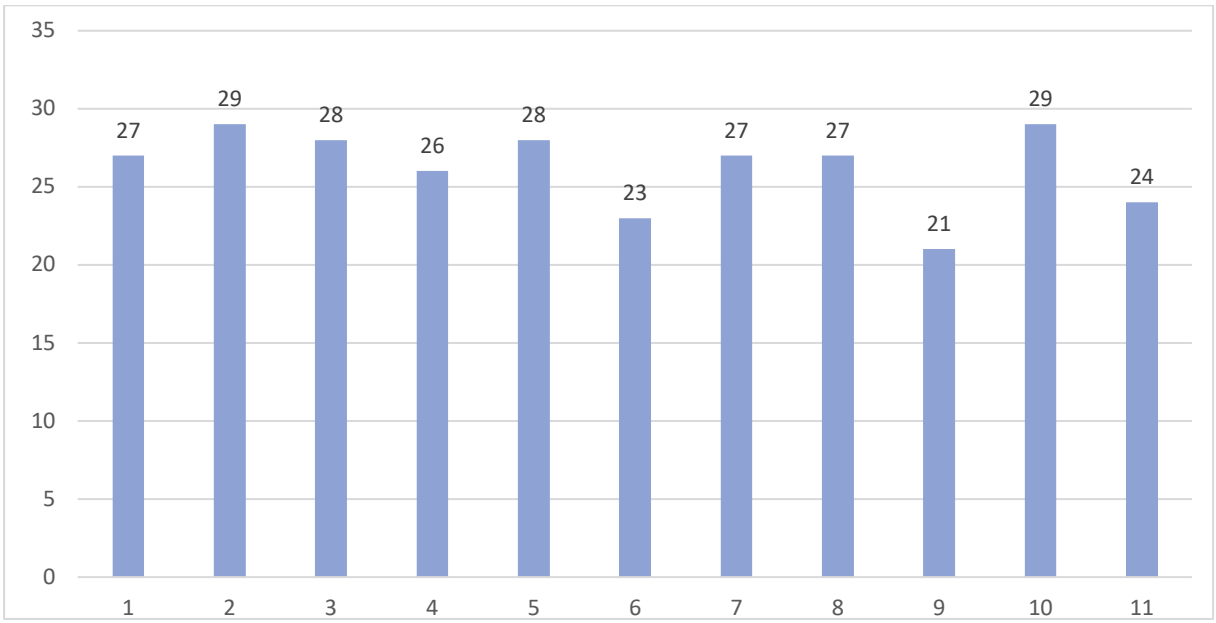

Figure 3.

Graphical presentation of CONSORT compliance per item

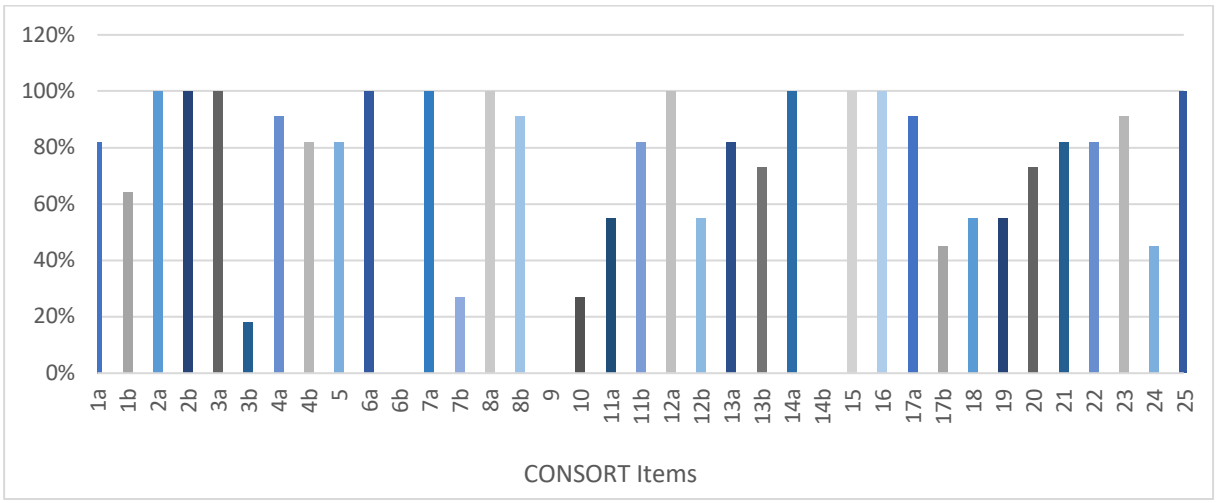

Figure 4.

Correlation (scatter-plot) between reporting quality and Impact Factor (IF)