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META-ANALYSIS

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Reparixin improves survival in critically ill and transplant patients: A meta-analysis

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Abstract

Background: Reparixin, an anti-inflammatory drug that inhibits interleukin 8 (IL-8) activity, might be life-saving for high-risk in-hospital patients without increasing the risk of infection according to a previous meta-analysis. With the increasing availability of randomised data the aim of the current study is to update previous findings by including any randomised control trials (RCTs) investigating the impact of reparixin on survival of critically ill or transplant patients.

Methods: A search strategy was developed to identify all RCTs involving reparixin in critically ill or transplant patients, with the exclusion of oncological patients. Two trained and independent authors conducted a thorough search of relevant databases. In addition, backward snowballing was employed. Language restrictions were not imposed.

Results: Our analysis included a total of nine studies involving 733 patients: 437 received reparixin and 296 the comparator. The reparixin group had a significantly lower all-cause mortality rate compared to the control group [15/437 (3.4%) vs. 19/294 (6.4%), odds ratio = 0.47 (95% confidence interval 0.23–0.96), *p*-value for effect .04, I2 = 22%, number needed to treat = 33]. These findings had the same direction and magnitude of effect across COVID-19 patients ($n = 325$) and non-COVID-19 patients ($n = 408$). Furthermore, there were no significant differences in the rate of pneumonia, sepsis or non-serious infections between the two groups.

Conclusions: The findings of this meta-analysis indicate that reparixin, an anti-inflammatory drug, improved survival in critically ill or transplant patients (including both COVID-19 and non-COVID-19 patients) without increasing the risk of infection.

KEYWORDS

COVID-19, critical care, intensive care, pneumonia, reparixin, transplantation

1 | INTRODUCTION

The human body's innate immune system heavily relies on neutrophils as the first-line defence against infections. During infection, pro-inflammatory cytokines such as CXCL8 (IL-8) are necessary for neutrophil recruitment and migration to inflamed sites.[1,2] However, an exaggerated and persistent pro-inflammatory activation of neutrophils can result in severe tissue damage, leading to clinical complications in critically ill patients and to transplant rejection.[3–5] Rejection is the main cause of graft loss during the first year[6] and the deleterious role of the immune system in this process is now well known. In particular, the release of pro-inflammatory cytokines damages the endothelium leading to platelet activation, activation of the coagulation system, thrombosis and finally to irreversible ischemic necrosis of the transplanted organ.[7] This response is known as systemic inflammatory response syndrome (SIRS), which aims to eliminate the source of the insult, whether endogenous or exogenous.[8] If an infection is suspected, SIRS is termed sepsis.[8] Despite its defensive purpose, an overabundant release in situ of cytokines by activated neutrophils, resident macrophages and monocyte, lead to a critical condition called *cytokine storm* in which cytokines spread throughout the entire body causing systemic effects and collateral damage to vital organ system.[9] Hyperinflammation resulting from cytokine storm is the primary culprit in multiorgan failure (MOF), the most common cause of morbidity and mortality in critically ill patients.[10] Critical manifestations of MOF include acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC).[11] Interestingly, the same cascade of events implicated in the aforementioned process is also involved in the pathogenesis of COVID-19 as a result of SARS-CoV-2 infection, leading to severe respiratory disease and unfavourable outcomes in COVID-19 patients.[12–14]

Reparixin is an allosteric inhibitor of the interleukin 8 (IL-8) receptors CXCR1 and CXCR2, and our previous meta-analysis suggested that its anti-inflammatory properties could improve survival of patients at high risk for in-hospital mortality.[15] Its efficacy and tolerance have been proven, and it has been successfully used to treat COVID-19-related acute respiratory distress syndrome (ARDS) and acute lung injury (ALI).[16,17] Although there are other anti-cytokines that have been approved, such as tocilizumab (a monoclonal antibody against the IL-6 receptor) and anakinra (an IL-1 receptor antagonist), their use raises concerns about immunosuppression, which can increase the risk of infections.[18,19] This is because they interact with the receptors in a competitive manner, leading to a decrease in the generation and mobilisation of neutrophils and resulting in neutropenia.[18,19] In contrast, the allosteric action of reparixin is 'permissive' as it blocks some of the effects induced by the endogenous ligand without affecting others.[20] Specifically, reparixin inhibits CXCR1/2 activation by IL-8 without blocking IL-8 binding to receptors. As evidence of this, many studies showed that reparixin is not associated with a reduction of neutrophils level[21,22] and does not increase the risk of infections.[15]

In the hypothesis that reparixin reduces the risk of mortality in critically ill and transplant patient without increasing the risk of infections, the aim of this study was to examine the effectiveness and safety of reparixin in critically ill or transplant patients by analysing the outcomes of any randomised controlled trial ever performed.

2 | METHODS

2.1 | Search strategy and study selection

We have updated our previous meta-analysis[15] by conducting a search of PubMed, EMBASE, ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies. Given the limited number of studies available, our search strategy was focused on using the keywords reparixin or repertaxin. This study was registered at Open Science Framework Registries on 14 September 2022 (Registration DOI: 10.17605/OSF.IO/DR5VT), and the PRISMA checklist is presented in Figure 1.

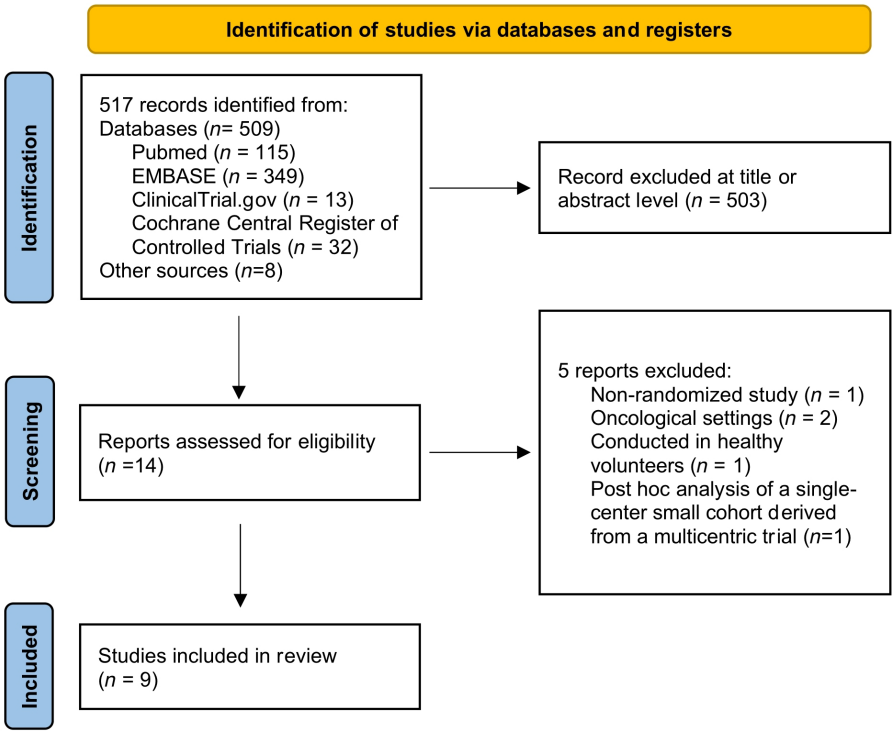
Our inclusion criteria consisted of randomised controlled trials (RCTs) involving critically ill (e.g. pancreatitis, COVID-19 sepsis, trauma, shock, pulmonary illness, cardiac surgery) or transplant patients that compared reparixin to any other treatment, without restrictions on dose or time of administration. Studies involving oncological patients or non-adult patients were excluded. Backward snowballing was applied to retrieve additional manuscripts and international experts were contacted for additional studies. Abstract of recent (last 3 years) international congresses were searched. No language restrictions were imposed.

Two independent investigators screened titles and abstracts of identified studies, with discrepancies resolved by a third author. Relevant studies were then assessed for eligibility, with compliance to selection criteria determined by two independent investigators and any discrepancies resolved by consensus. Searches are updated on 20 December 2023.

2.2 | Data extraction

Data extraction were performed by two independent authors who collected baseline, procedure and outcome

FIGURE 1 Prisma flow diagram.



data. They followed the intention-to-treat principle whenever possible and contacted corresponding authors by email to obtain any missing data. The primary endpoint of the review was the mortality rate at the longest follow-up available. Secondary endpoints were the risk of pneumonia, sepsis and non-serious infections.

2.3 | Assessment of risk of bias

To assess the risk of bias in randomised studies, the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2)[23] was used and any divergences were resolved by consensus. Publication bias was evaluated by visually inspecting funnel plots.

2.4 | Data analysis

We calculated the odds ratio (OR) with a 95% confidence interval (CI) for dichotomous variables and the risk ratio (RR) with a 95% CI for common events, which were defined as events occurring in the control group with a frequency greater than 25%. We determined the proportion of patients with the outcome in each group and calculated the *p*-value for the comparison between the groups. A *p*-value ≤.05 was considered statistically significant. Additionally, we calculated the number needed to treat (NNT). We used a fixed effect model or a random-effect model, depending on the level of statistical inconsistency ($I2 < 25\%$ or $I2 > 25\%$, respectively) to account for clinical and statistical variations. We performed sensitivity analyses by comparing the results of a fixed effects versus a random-effects model, changing the summary statistics (odds ratios, risk differences or risk ratios), or removing each study in turn. We conducted the meta-analysis using Review Manager software (RevMan, version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020).

Reporting of the study conforms to broad EQUATOR guidelines (Simera et al. A catalogue of reporting guidelines for health research. Eur J Clin Invest. 2010 Jan;40(1):35–53).

3 | RESULTS

A total of 14 articles were retrieved through database searches, expert contacts and snowballing. However, five studies were excluded based on our predefined exclusion criteria. One study was not randomised,[21] two included cancer patients,[22,24] one was conducted in healthy volunteers,[25] and one[26] was a post-hoc analysis of a small single-centre cohort derived from a multicentric trial.[27] Overall, nine studies[16,17,27–33] were included in this meta-analysis, with a total of 733 randomised patients, of which 437 received reparixin and 296 received the comparator.

3.1 | Trials' characteristics

Trials included in this meta-analysis were conducted in North America and Europe between 2008 and 2022. Studies were conducted in various patient populations, including solid organ transplant recipients (three trials, 215 patients),[28,30,31] patients with type one diabetes receiving pancreatic islet transplantation (two trials, 57 patients),[27,33] patients with severe COVID-19 pneumonia[16,17] (two trials, 325 patients), patients with severe chronic or recurrent acute pancreatitis undergoing total pancreatectomy with islet autotransplantation,[32] and patients undergoing on-pump coronary artery bypass grafting[29] (one trial each with 104 and 32 patients, respectively) (Table 1).

The most commonly administered dose was an intravenous infusion of 2.8 mg/kg/h, and the most frequently used length of administration was 1 week. The majority of trials (seven trials, 638 patients) used placebo as control treatment, while the other two trials used standard care as control (Table 2).

3.2 | Quantitative data synthesis

3.2.1 | Primary endpoint

The forest plot displayed in Figure 2 shows the effect of reparixin on mortality, based on data from the nine randomised studies included in this meta-analysis. The results indicate that patients who received reparixin had a significantly lower mortality rate than those in the control group, with 15 out of 437 patients (3.4%) in the reparixin group and 19 out of 296 patients (6.4%) in the control group experiencing mortality, OR 0.47 (95% confidence

TABLE 1 Description of the studies included in the meta-analysis, in order of year of publication.

First author	Year	Journal	Country[a]	Setting	Pts age (mean ± SD) reparixin group	Pts age (mean ± SD) control group
Meyers BF	2008	J Heart Lung Transplant	United States, Canada and Italy	Primary graft dysfunction in lungs transplantation	NA	NA
Citro A	2012	J Clin Invest	Italy and Germany	Pancreatic islet transplantation in type 1 diabetes	48.5 ± 5	48.0 ± 4
Opfermann P	2015	Clin Exp Immunol	Austria	Ischaemia-reperfusion injury and inflammation after on-pump coronary artery bypass graft surgery	65 ± 5.5	66 ± 6.5
Zhuravel SG	2017	ClinicalTrial.gov	Russian Federation and Belarus	Orthotopic liver transplantation	NA	NA
Maffi P	2020	Diabetes Care	Italy, Sweden, United Kingdom, Czech Republic and United States	Pancreatic islet transplantation in type 1 diabetes	46.9 ± 11.5	41.2 ± 8.9
Remuzzi G	2020	ClinicalTrial.gov	Italy, United States, France and Spain	Ischemia–reperfusion injury kidney transplantation	Group 1: 54.4 ± 7.4, group 2: 55.9 ± 6.3	51.4 ± 11.3
Witkowski P	2021	Am J Transplant	United States, Canada and Italy	Pancreatectomy for chronic pancreatitis	40 ± 14.4	39 ± 10
Landoni G	2022	Infect Dis Ther	Italy	COVID-19	60.6 ± 13.5	63.6 ± 14.2
Landoni G 2	2022	Abstract European Respiratory Society (ERS) Congress	Italy, United States	COVID-19	61.3 ± 11.8	60.0 ± 12.0

[a]The first country refers to the country of the corresponding author.

TABLE 2 Doses and modalities of administration of reparixin in the nine included randomised studies.

First author	Start time of administration	Posology (mg/kg/h) iv or per os	Length of treatment
Meyers BF	NA	2.8 mg/kg/h, iv	48 hours
Citro A	24 h before islet transfusion	2.8 mg/kg/h, iv	7 days
Opfermann P	After anaesthesia induction	4.5 mg/kg/h for 30 min followed by continuous infusion at 2.8 mg/kg/h until 8 h after the end of CPB, iv	8 hours
Zhuravel SG		2.8 mg/kg/h, iv	7 days
Maffi P	12 h before each islet transfusion	2.8 mg/kg/h, iv	7 days
Remuzzi G	12 h or 22.5 h before renal transplant	Variable doses, iv	<1 day
Witkowski P	24 h before islet transfusion	2.8 mg/kg/h administered at 0.25 mL/kg/h, iv	7 days
Landoni G	Hospitalised patients with COVID-19 pneumonia	3600 mg/d, os, (1200 mg, three times a day)	7 days
Landoni G	Hospitalised patients with COVID-19 pneumonia	3600 mg/d, os (1200 mg, three times a day)	21 days

Abbreviations: iv, intravenous; os, orally.

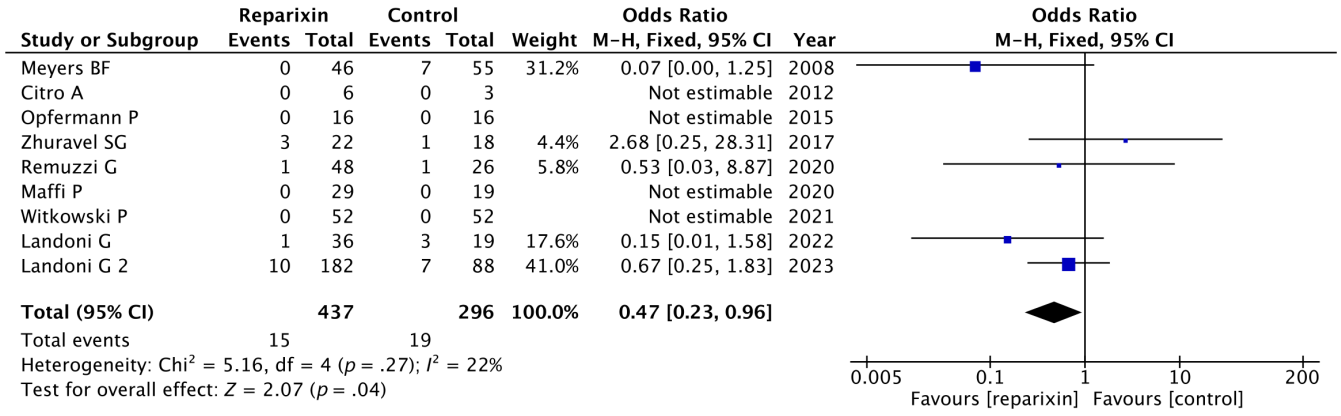


FIGURE 2 Forest plot of the effect of reparixin on mortality.

interval 0.23–0.96 *p*-value for efficacy = .04, I2 22%, number needed to treat = 33). No small study bias was detected upon visual inspection of the funnel plot (Figure S1). Sensitivity analyses, including subgroups of patients with COVID-19 and non-COVID-19, transplant patients, perioperative settings and length of treatment ≥48 h, confirmed the direction and magnitude of these findings (Figures S5–S10). Additionally, the risk of bias analysis revealed that six of the included studies, accounting for 629 patients, were at a low risk of bias, while three trials were identified as to have some concerns in the overall risk of bias assessment (Figure S11).

3.2.2 | Secondary endpoints

In our analysis, we observed a tendency towards a decrease in the incidence of pneumonia among patients treated with reparixin compared to controls. Specifically, 4 out of 311 patients (1.3%) in the reparixin group developed pneumonia compared to 9 out of 185 patients (4.9%) in the control group, with an odds ratio (OR) of 0.39 [95% CI 0.14–1.08], *p* for effect = .07, and I2 = 0%, based on four trials (see Figures 3 and S2). No significant differences were detected between the two groups in terms of the incidence of sepsis (5 of 311 [1.6%] in the reparixin

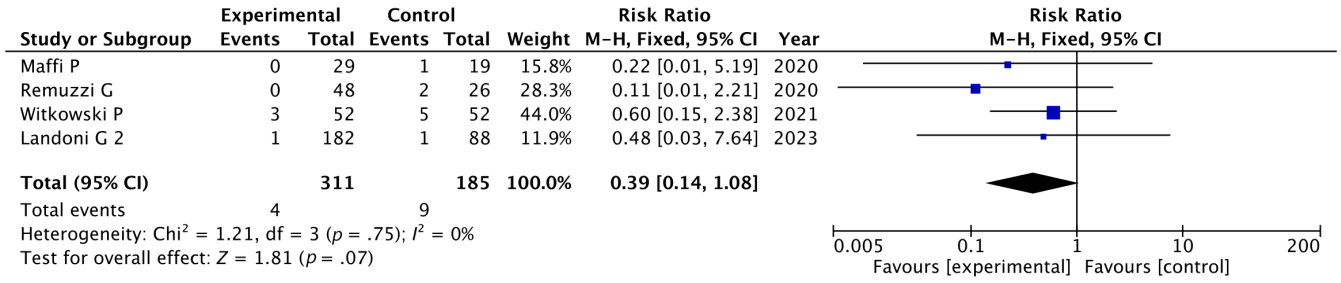


FIGURE 3 Forest plot of the effect of reparixin on developing pneumonia.

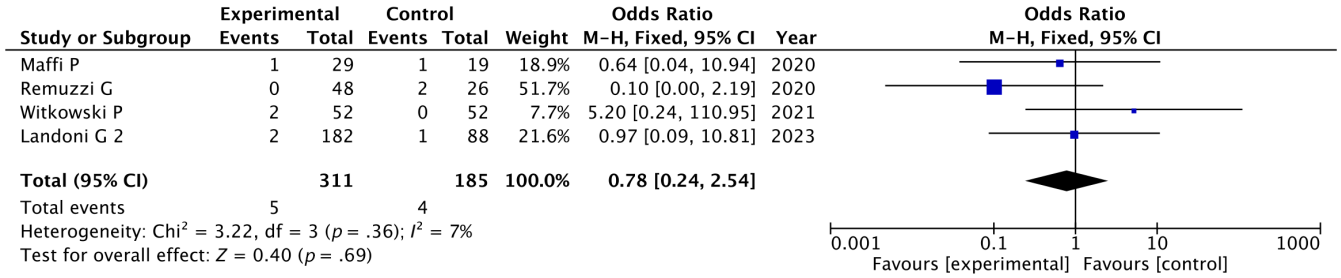


FIGURE 4 Forest plot of the effect of reparixin on developing sepsis.

group vs. 4 of 185 [2.2%] in the control group, OR = 0.78 [95% CI 0.24–2.54], *p* for effect = .36, I2 = 7%, four trials included; see Figures 4 and S3) and non-serious infections (38 of 327 [11.6%] in the reparixin group vs. 29 of 201 [14.4%] in the control group, OR = 0.72 [95% CI 0.43–1.22], *p* for effect = .22, I2 = 0%, five trials included; see Figures 5 and S4).

4 | DISCUSSION

4.1 | Key findings

This meta-analysis confirmed that the administration of reparixin reduces mortality in high-risk patients with an inflammatory status without increasing the risk of major or minor infections.

4.2 | Relationship to previous studies

We expanded our previous study[15] to include three additional studies, which almost doubled the number of included patients. Two of these studies were conducted in transplant patients,[27,33] and one was recently published and focused on COVID-19 patients.[17] By including these new studies, we were able to reinforce our previous findings on the safety and efficacy of reparixin, particularly in relation to the risk of developing pneumonia, sepsis or other non-serious infections. In total, we evaluated the safety of reparixin in 496 patients, compared to the 178 patients in our previous meta-analysis. The results confirmed that reparixin does not increase the risk of infection and may even lower the rate of pneumonia among patients.

When compared to other cytokine inhibitors, such as tocilizumab and anakinra, which demonstrated efficacy in the treatment of COVID-19,[34,35] reparixin has also been studied in other settings and has shown promising beneficial effects in critically ill and perioperative patients. While the benefits of tocilizumab and anakinra are primarily limited to COVID-19 patients, reparixin may have wider applications beyond this specific setting.

4.3 | Significance of study findings and what this study adds to our knowledge

What is noteworthy is that reparixin not only reduced mortality, but it also did not increase the risk of infection in critically ill patients who are highly susceptible to severe and potentially fatal infections. Therefore, further research should be conducted on its clinical use in major surgery settings and in critically ill patients, including those with COVID-19.

Moreover, our meta-analysis remarks the importance of anti-inflammatory drugs in the treatment of critically ill and perioperative patients. In fact, the immune response of these patients often turns from defensive to seriously dangerous, frequently leading to death. In these cases, activated immune cells, of which neutrophils are the main

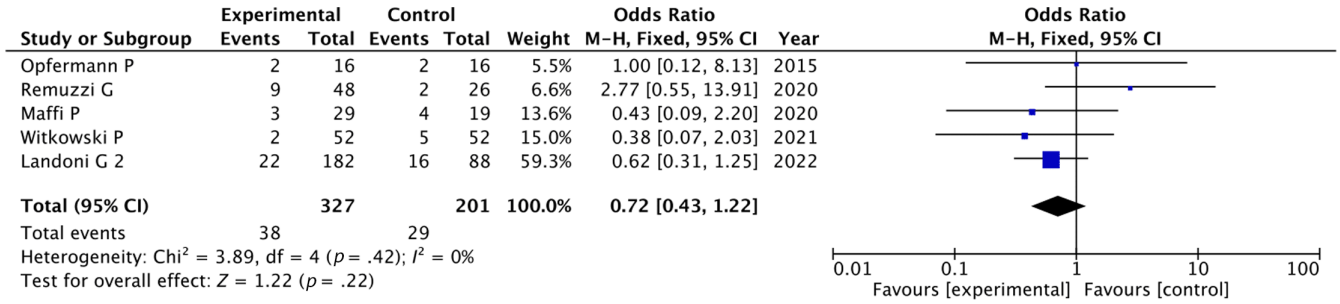


FIGURE 5 Forest plot of the effect of reparixin on the occurrence of a non-serious infection.

players, produce and secrete pro-inflammatory cytokines that further worsen tissue damage. Blocking these pathways has shown remarkable clinical utility by greatly reducing deaths in comparison with placebo group.[15,36]

4.4 | Strengths and limitations of the study

The main limitation of our study is the relatively small sample size, despite the inclusion of nine studies. The limited number of events prevents us from drawing definitive conclusions. Furthermore, not all studies have been published in full format as a research paper, some of the studies had a small number of participants, and the age range within the study population was restricted. Nevertheless, all included studies were randomised, and some of them were multicentre trials. Additionally, the funnel plot demonstrated no evidence of publication bias in small studies. All included studies were conducted in critical or perioperative settings, and not only overall showed a reduction of mortality in the intervention group, but also trends in the same directions were observed in almost every subgroup analysed, suggesting that the anti-inflammatory properties of reparixin may be beneficial in various settings.

4.5 | Future studies and prospects

Based on the results of our meta-analysis, future studies should further test the effects of administration of reparixin to both COVID-19 and non-COVID-19 patients. Indeed, an ongoing large, multicentre RCT[37] is evaluating efficacy and safety of oral reparixin versus standard care in limiting disease progression in 526 adult patients hospitalised for infectious pneumonia acquired in the community, including COVID-19. Another multicentre RCT is currently investigating the effect of reparixin in 66 non-COVID-19 ARDS.[38]

Moreover, the results of our study suggest that reparixin could be further studied in the perioperative settings of major surgery to reduce the systemic inflammatory response and postoperative complications. Notably, the promising findings on infection risk suggest that reparixin does not increase the risk of infection and may even reduce the rate of patients developing pneumonia.

5 | CONCLUSIONS

Our meta-analysis provides evidence supporting the life-saving benefits of reparixin, an IL-8 receptor inhibitor, in critically ill patients including those with COVID-19, transplant recipients and those undergoing major surgery. Importantly, our findings also suggest that reparixin does not increase the risk of infections and may even decrease the incidence of pneumonia.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REFERENCES

1. Lee SK, Kim SD, Kook M, et al. Phospholipase D2 drives mortality in sepsis by inhibiting neutrophil extracellular trap formation and down-regulating CXCR2. *J Exp Med*. 2015;212:1381-1390. doi:10.1084/jem.20141813
2. Shen X-F, Zhao Y, Cao K, et al. Wip1 deficiency promotes neutrophil recruitment to the infection site and improves sepsis outcome. *Front Immunol*. 2017;8:1023. doi:10.3389/fimmu.2017.01023

3. Castanheira FVS, Kubes P. Neutrophils and NETs in modulating acute and chronic inflammation. *Blood*. 2019;133(20):2178-2185. doi:10.1182/blood-2018-11-844530
4. Grégoire M, Uhel F, Lesouhaitier M, et al. Impaired efferocytosis and neutrophil extracellular trap clearance by macrophages in ARDS. *Eur Respir J*. 2018;52(2):1702590. doi:10.1183/13993003.02590-2017
5. Lenz M, Draxler DF, Zhang C, et al. Toll-like receptor 2 and 9 expression on circulating neutrophils is associated with increased mortality in critically ill patients. *Shock*. 2020;54(1):35-43. doi:10.1097/SHK.0000000000001467
6. Cozzi E, Colpo A, De Silvestro G. The mechanisms of rejection in solid organ transplantation. *Transfus Apher Sci*. 2017;56(4):498-505. doi:10.1016/j.transci.2017.07.005
7. Yu S, Lu J. Macrophages in transplant rejection. *Transpl Immunol*. 2022;71:101536. doi:10.1016/j.trim.2022.101536
8. Chakraborty RK, Burns B. Systemic inflammatory response syndrome. *StatPearls [Internet]*. StatPearls Publishing; 2022.
9. Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med*. 2020;383(23):2255-2273. doi:10.1056/NEJMra2026131
10. Kozlov AV, Grillari J. Pathogenesis of multiple organ failure: the impact of systemic damage to plasma membranes. *Front Med (Lausanne)*. 2022;15(9):806462. doi:10.3389/fmed.2022.806462
11. Marshall JC. The multiple organ dysfunction syndrome. In: Holzheimer RG, Mannick JA, eds. *Surgical Treatment: Evidence-Based and Problem-Oriented*. Zuckschwerdt; 2001.
12. Veras FP, Pontelli MC, Silva CM, et al. SARS-CoV-2–triggered neutrophil extracellular traps mediate COVID-19 pathology. *J Exp Med*. 2020;217(12):e20201129. doi:10.1084/jem.20201129
13. Masso-Silva JA, Moshensky A, Lam MT, et al. Increased peripheral blood neutrophil activation phenotypes and NETosis in critically ill COVID-19 patients: a case series and review of the literature. *Clin Infect Dis*. 2021;74:479-489. doi:10.1093/cid/ciab437
14. Li H, Zhang J, Fang C, et al. The prognostic value of IL-8 for the death of severe or critical patients with COVID-19. *Medicine*. 2021;100(11):e23656. doi:10.1097/MD.0000000000023656
15. Landoni G, Zangrillo A, Piersanti G, Scquizzato T, Piemonti L. The effect of reparixin on survival in patients at high risk for in-hospital mortality: a meta-analysis of randomized trials. *Front Immunol*. 2022;25(13):932251. doi:10.3389/fimmu.2022.932251
16. Landoni G, Piemonti L, Monforte AD, et al. A multicenter phase 2 randomized controlled study on the efficacy and safety of Reparixin in the treatment of hospitalized patients with COVID-19 pneumonia. *Infect Dis Ther*. 2022;26:1-16. doi:10.1007/s40121-022-00644-6
17. Landoni G, Voza A, Puoti M, et al. *A phase 3 study to evaluate the efficacy and safety of Reparixin in severe COVID-19 pneumonia*. Barcellona, Spain: European Respiratory Society (ERS) Congress; 2022.
18. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med*. 2021;27(10):1752-1760. doi:10.1038/s41591-021-01499-z
19. Wang D, Fu B, Peng Z, et al. Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. *Front Med*. 2021;15(3):486-494. doi:10.1007/s11684-020-0824-3
20. Kenakin TP. Biased signalling and allosteric machines: new vistas and challenges for drug discovery. *Br J Pharmacol*. 2012;165(6):1659-1669. doi:10.1111/j.1476-5381.2011.01749.x
21. Schott AF, Goldstein LJ, Cristofanilli M, et al. Phase ib pilot study to evaluate reparixin in combination with weekly paclitaxel in patients with HER-2-negative metastatic breast cancer. *Clin Cancer Res*. 2017;23(18):5358-5365. doi:10.1158/1078-0432.CCR-16-2748
22. Goldstein LJ, Perez RP, Yardley D, et al. A window- of-opportunity trial of the CXCR1/2 inhibitor reparixin in operable HER-2-negative breast cancer. *Breast Cancer Res*. 2020;22(1):4. doi:10.1186/s13058-019-1243-8
23. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l489. doi:10.1136/bmj.l4898
24. ClinicalTrial.gov NCT02370238. A Double-Blind Study of Paclitaxel in Combination with Reparixin or Placebo for Metastatic Triple-Negative Breast Cancer (FRIDA). https://clinicaltrials.gov/ct2/show/NCT02370238.
25. Leitner JM, Mayr FB, Firbas C, et al. Reparixin, a specific interleukin-8 inhibitor, has no effects on inflammation during endotoxemia. *Int J Immunopathol Pharmacol*. 2007;20(1):25-36. doi:10.1177/039463200702000104
26. Bachul PJ, Golab K, Basto L, et al. Post-hoc analysis of a randomized, double blind, prospective study at the university of Chicago: additional standardizations of trial protocol are needed to evaluate the effect of a CXCR1/2 inhibitor in islet allotransplantation. *Cell Transpl*. 2021;30:9636897211001774. doi:10.1177/09636897211001774
27. Maffi P, Lundgren T, Tufveson G, et al. Targeting CXCR1/2 does not improve insulin secretion after pancreatic islet transplantation: a phase 3, double-blind, randomized, placebo-controlled trial in type 1 diabetes. *Diabetes Care*. 2020;43(4):710-718. doi:10.2337/dc19-1480
28. Meyers BF, Keshavjee S, Zamora MR, et al. 405: a multicenter prospective, randomized, placebo-controlled trial of a CXCL8 inhibitor (Reparixin) to prevent primary graft dysfunction after lung transplantation. *J Heart Lung Transpl*. 2008;27:S206-S207. doi:10.1016/j.healun.2007.11.417
29. Opfermann P, Derhaschnig U, Felli A, et al. A pilot study on reparixin, a CXCR1/2 antagonist, to assess safety and efficacy in attenuating ischaemia-reperfusion injury and inflammation after on-pump coronary artery bypass graft surgery. *Clin Exp Immunol*. 2015;180(1):131-142. doi:10.1111/cei.12488
30. ClinicalTrial.gov NCT03031470. Pilot Study of Reparixin for Early Allograft Dysfunction Prevention in Liver Transplantation. https://clinicaltrials.gov/ct2/show/NCT03031470
31. ClinicalTrial.gov NCT00248040. Reparixin in Prevention of Delayed Graft Function after Kidney Transplantation. https://clinicaltrials.gov/ct2/show/NCT00248040
32. Witkowski P, Wijkstrom M, Bachul PJ, et al. Targeting CXCR1/2 in the first multicenter, double-blinded, randomized trial in autologous islet transplant recipients. *Am J Transplant*. 2021;21(11):3714-3724. doi:10.1111/ajt.16695
33. Citro A, Cantarelli E, Maffi P, et al. CXCR1/2 inhibition enhances pancreatic islet survival after transplantation. *J Clin Invest*. 2012;122(10):3647-3651. doi:10.1172/JCI63089

34. Kooistra EJ, Waalders NJB, Grondman I, et al. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care*. 2020;24(1):688. doi:10.1186/s13054-020-03364-w
35. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2021;181(1):41-51. doi:10.1001/jamainternmed.2020.6252 Erratum in: JAMA Intern Med 2021 Apr 1;181(4):570.
36. Mantovani A, Garlanda C. Humoral innate immunity and acute-phase proteins. *N Engl J Med*. 2023;388(5):439-452. doi:10.1056/NEJMra2206346
37. ClinicalTrial.gov NCT05254990. Reparixin 1200 mg TID as add-on to SoC to limit disease progression in hospitalised patients with COVID-19 and other community-acquired pneumonia. A Multicentre, Randomised, Double-Blinded, Placebo-Controlled, Phase III Trial (REPAVID-22) https://clinicaltrials.gov/ct2/show/NCT05254990
38. ClinicalTrial.gov NCT05496868. Add-on Reparixin in Adult Patients With ARDS. https://clinicaltrials.gov/ct2/show/NCT05496868

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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