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Review Article

Effect of Levosimendan Treatment in Pediatric Patients With Cardiac Dysfunction: An Update of a Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Levosimendan increasingly has been used to treat heart failure and cardiac dysfunction in pediatric patients. Currently, there is only limited evidence that this drug positively affects outcomes. The authors' aim was to investigate the effects of levosimendan on hemodynamic parameters and outcomes in pediatric patients in all clinical settings. The study design was a systematic review of randomized and nonrandomized studies. Randomized clinical trials (RCTs) were included in a meta-analysis. The primary outcome of the meta-analysis was the effect of levosimendan on central venous oxygen saturation ($ScvO_2$) and lactate values as surrogate markers of low-cardiac-output syndrome. The study setting was any acute care setting. Study participants were pediatric patients (age <18 years) receiving levosimendan, and the intervention was levosimendan versus any control treatment. The authors identified 44 studies published from 2004 to 2020, including a total of 1,131 pediatric patients. Nine studies (enrolling 547 patients) were RCTs, all performed in a pediatric cardiac surgery setting. Three RCTs were judged to carry a low risk of bias. In the RCTs, levosimendan administration was associated with a significant improvement of $ScvO_2$ ($p = 0.03$) and a trend toward lower postoperative lactate levels ($p = 0.08$). No differences could be found for secondary outcomes. Levosimendan use in pediatric patients is not associated with major side effects and may lead to hemodynamic improvement after cardiac surgery. However, its impact on major clinical outcomes remains to be determined. Overall, the quality of evidence for levosimendan use in pediatric patients is low, and further high-quality RCTs are needed.

Key Words: children; heart failure; levosimendan; simdax; cardiac surgery

LEVOSIMENDAN IS AN INODILATOR agent known to improve cardiac function, hemodynamic performance, and, possibly, survival in critically ill patients.[1] In contrast to traditional inotropic agents, which exert their positive inotropic effect by increasing cyclic adenosine monophosphate and intracellular calcium levels, negatively raising myocardial energy requirements,[2] levosimendan promotes cardiac contractility by increasing the sensitivity of myofibrils to calcium during systole.[3,4] This unique mechanism offers the advantage to avoid myocardial oxygen consumption and the potential consequent risk of arrhythmias and myocardial injury.[5-7] In addition, levosimendan exerts a cardioprotective effect by opening the mitochondrial potassium channels of cardiomyocytes.[8] Levosimendan has a unique pharmacokinetic profile because its metabolites (odds ratio−1896) are more active than the drug itself, allowing a prolonged inotropic effect lasting for at least seven days.[9]

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The majority of studies showing beneficial effects of levosimendan have been performed in adults. In the pediatric setting, heart failure and low-cardiac-output syndrome (LCOS) may occur as complications of different conditions. In particular, LCOS occurs in nearly 25% of patients after congenital cardiac surgery.[10] Early studies showed that levosimendan could be administered safely in neonates and children, allowing a reduction in catecholamine infusion and improving myocardial function.[11,12] Nevertheless, its use is still off-label for this specific patient population.[13] The authors, therefore, performed an update of their previous systematic review[14] on the use of levosimendan in pediatric patients and performed a meta-analysis of the randomized controlled trials (RCTs) to elucidate the evidence regarding its use. The primary outcome was the effect of levosimendan on central venous oxygen saturation ($ScvO_2$) and lactate values as surrogate markers of LCOS in pediatric patients. Secondary outcomes included cardiac biomarkers, mortality, and length of intensive care unit (ICU) and hospital stay.

Methods

Bio Med Central, PubMed, Embase, and the Cochrane Central Register of clinical trials were searched for pertinent studies (updated December 31, 2020) by two investigators (S.S., S. B.), using only the term "levosimendan or simdax." Further search involved conference and congress proceedings. The references of retrieved articles were checked carefully to identify further pertinent articles.

This manuscript adheres to the applicable Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Study Selection

References obtained from the database and literature first were examined independently at the title and/or abstract level by two investigators (S.S., S.B.), and then, if potentially pertinent, retrieved as complete articles. The studies were selected if they described the administration of levosimendan in pediatric patients, including neonates (one-30 days), infants (one-12 months), and children (one-$\leq$18 years) in any setting. The exclusion criteria included: age $>$18 years, review, or meta-analysis and basic research. No language restriction was enforced.

Two investigators (S.S., A.B.) selected studies for the final analysis and independently assessed compliance to selection criteria. Divergences were resolved by consensus. Only RCTs were included in the meta-analysis.

Data Abstraction and Study Characteristics

All data were extracted independently by two investigators (S.S., S.B.). A consensus was obtained between both investigators whenever the findings were divergent. For each study, the following information was selected: authors, year of publication, year of enrollment, the total number of participants, age, country of publication, study design, clinical setting and/or indication, bolus and infusion doses of levosimendan, duration of levosimendan treatment, control treatment, hemodynamic data (cardiac index, ejection fraction), $ScvO_2$ and lactate levels, B-type natriuretic peptide (BNP)/N-terminal-pro hormone BNP (NT-proBNP), troponin for both levosimendan and control group, mortality, ICU stay, hospital stay, and adverse events.

The authors performed a meta-analysis of RCTs comparing levosimendan versus any control treatment in all clinical settings, using the previously described methodology. Primary outcomes for the meta-analysis were the post randomization $ScvO_2$ and lactate values as surrogate markers of LCOS. Secondary outcomes were the postoperative BNP/NT-proBNP and troponin levels, longest follow-up mortality, ICU and hospital stays.

Statistical Analysis

For dichotomous outcomes, the authors calculated individual and pooled risk ratios, with 95% confidence intervals (CI). For continuous variables, the mean difference (MD) or standardized mean difference (SMD) with corresponding 95% CI were calculated. MD was used for variables expressed in the same unit of measurement, whereas SMD was used for variables expressed in different units of measurement. The authors converted continuous variables, reported as median and interquartile range or median and range, into mean and standard deviation following the methodology described by Wan et al.[15]

Serum lactate, troponin, and BNP/NT-proBNP units of measurement were analyzed as reported by original individual studies. Length of ICU and length of hospital stays were presented in days. Whenever original studies expressed length of ICU stay in hours, this was converted to days.

The authors performed heterogeneity analysis with Cochran Q statistic and quantified statistical heterogeneity with I^2. They considered heterogeneity with an $I^2 > 25\%$ as significant. The authors employed the fixed-effect model in case of low statistical heterogeneity, while the random-effects model was used in case of high statistical heterogeneity.

The authors assessed publication bias for the primary endpoint with a visual assessment of funnel plot if the number of analyzed studies was $>$ten.[16,17] For pooled outcome analyses, they considered a p value $\leq$0.05 as significant.

The risk of bias of RCTs included in the meta-analysis was assessed following the recommended seven- items tool of Cochrane Collaboration (randomized sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, other bias).[17,18] An overall judgment of low, high, or unclear risk of bias was provided.

The following sensitivity analyses were performed for significant outcomes: low risk of bias trials only, sequential removal of each individual trial and reanalysis of the remaining dataset, change of analysis methods, and change of summary statistics.

The statistical analysis was performed using RevMan 5.3. Software (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

The literature search yielded a total of 1,810 titles. Excluding 1,052 nonpertinent titles (review or meta-analysis, adult subjects, animals research), 758 abstracts were evaluated. Excluding 713 abstracts that, according to the selection criteria, were considered nonpertinent, a total of 45 studies were considered. One study was excluded[19] because of inclusion in a previous broader manuscript.[20] Two studies were published as abstract only[21,22] and were not considered. Forty-four articles finally were included in this systematic review (Figure 1).[9,11,12,13,20-58] Only nine studies[11,13,29,32,38,40,57,58] were RCTs, and all of these were performed in cardiac surgery settings. These studies were included in this meta-analysis.

Study Characteristics

The details of the 44 selected studies are described in Supplementary Table 1. The 44 selected studies included a total of 1,131 pediatric patients who received levosimendan as treatment.

Overall studies were published in the period between 2004 and 2020, and patients' enrollment was performed between 2001 and 2019. No study was multicenter, and the majority (30 studies, 68.2%) were conducted in Europe. These studies included pediatric patients with various causes of cardiac dysfunction, mainly after cardiac surgery (31 studies, 69.8%). Other causes of cardiac dysfunction were chronic cardiac conditions, septic shock, or cancer.

Compared with the authors' previous systematic review, which included studies from 2004 to 2014,[14] the current systematic review (updated on December 2020) found 20 new publications, including 508 new patients. Over the past six years, levosimendan has been used increasingly in the cardiac setting.[9,43,46,47,50,52,54] In addition, an increasing number of trials have described its repetitive administration.[9,43,50,54]

Different comparators were used in the nine RCTs: placebo in two studies,[13,58] standard treatment in one study,[11] dobutamine in one study,[38] and milrinone in five studies.[12,32,35,40,57] In total, 547 patients received the study medication among these nine RCTs; 277 were randomized to the levosimendan group and 270 to the control group. Table 1 provides detailed information about the mode and the timing of the administration of the study drug in these RCTs. In four studies, a levosimendan bolus was followed by continuous infusion, ranging between 0.05 and 0.2 μg/kg/min. In one study, a levosimendan infusion was administered prophylactically in the preoperative period.[58] The dose regimen and schedule for levosimendan administration varied among studies (Table 1).

Quantitative Data Synthesis

The authors' current meta-analysis of RCTs comparing levosimendan versus any comparator showed that levosimendan administration was associated with a significant improvement in post randomization $ScvO_2$ (MD = 4.88; 95% CI = 0.45-to-9.32; p = 0.03; I^2 = 0%; two studies included; Figure 2).

Furthermore, in the levosimendan group, the authors observed a trend towards lower postoperative lactate levels (SMD = −0.37; 95% CI = −0.79 to 0.05; p = 0.08; I^2 = 68%; five studies included; Figure 3).

The authors found no significant differences in terms of postoperative BNP/NT-proBNP (Supplementary Figure 1) or troponin levels (Supplementary Figure 2). Otherwise, no

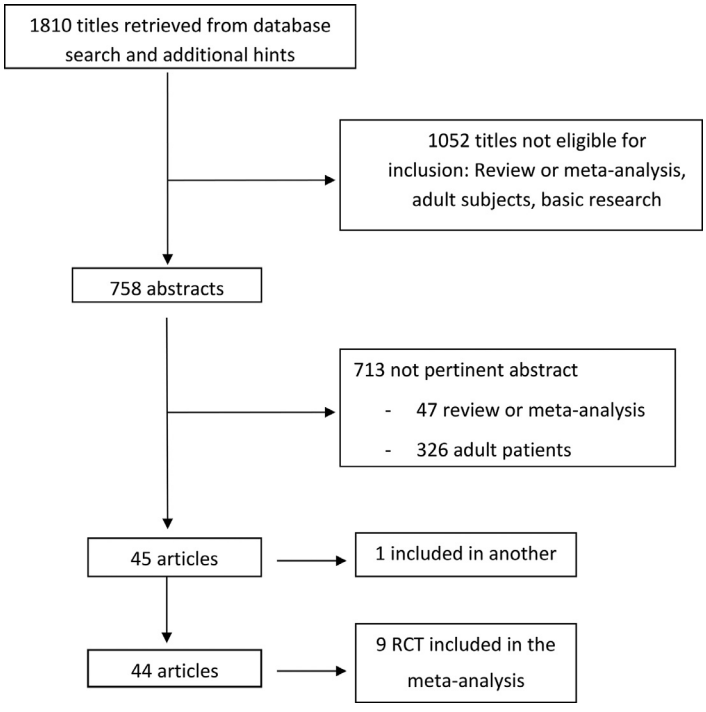

Fig. 1. A flowchart of included studies.

Table 1
Details of the Nine Randomized Controlled Trials Included in the Meta-Analysis.

Authors	Primary Endpoint	Drug Fontrol	N Randomized Patients	N Levo patients	N Control Patients	Levo bolus, $\mu g.kg^{-1}$	Levo infusion, $\mu g.kg^{-1}.min^{-1}$	Duration of Infusion, h
Ricci Z[11]	Incidence of postoperative LCOS	Standard inotropic management	63	32	31	None	0.1	72
Pellicer A[12]	Efficacy and safety of study drugs in newborns	Milrinone	20	11	9	0.1	0.15 then 0.2	48
Wang A[13]	Efficacy and safety of prophylactic Levosimendan use	Placebo	187	94	93	None	0.05	48
Momeni M[32]	Serum lactate levels at 4 h post-surgery	Milrinone	41	18	20	None	0.05	48
Lechner E[35]	Effect of prophylactically administered drug on cardiac index	Milrinone	40	19	20	None	0.1	24
Ebade AA[38]	Comparison of PAP and cardiac output after cardiac surgery	Dobutamine	50	25	25	15 over 10 minutes	0.1 - 0.2	NA
Himanshu S[40]	Effectiveness of intravenous levosimendan versus milrinone	Milrinone	50	25	25	12 over 10 minutes	0.1	NA
Thorlacius EM[57]	Effect of study drug on biventricular longitudinal strain	Milrinone	72	38	32	12	0.1	24
Molina AA[58]	Effect of preoperative levosimendan on postoperative cardiac biomarkers	Placebo	30	15	15	None	0.2	36 (12 preop and 24 postop)

Abbreviations: CPB, cardiopulmonary bypass; LCOS, low-cardiac output-syndrome; NA, not available; PAP, pulmonary artery pressure.

significant differences were found in terms of various outcome variables, such as length of stay in the ICU or in the hospital and mortality (Supplementary Figures 3, 4, and 5).

Risk of Bias

Overall, three RCTs were judged to carry a low risk of bias, one study had an unclear risk of bias, and five studies were considered at high risk of bias, generally due to lack of blinding (Figures 4 and 5).

Analysis of funnel plot was not performed, as the number of retrieved RCTs was lower than ten.

Sensitivity Analyses

As only two studies were included in the $ScvO_2$ analysis, the authors did not perform a sequential trial removing for this outcome. The change of analysis method from a fixed- to the random-effects model did not affect the results. Both studies included in the $ScvO_2$ analysis were considered as high-risk-of-bias studies.

Discussion

This is the most updated systematic review and meta-analysis on levosimendan use in pediatric patients.[14,59-61] No previous systematic review included all studies performed in pediatric patients. Furthermore, previous meta-analyses included a lower number of studies and patients.

In this systematic review and meta-analysis, the authors found that the use of levosimendan in pediatric patients has increased significantly over the last six years. Furthermore, similar to the adult population,[62] the use of repetitive levosimendan doses has gained popularity in the pediatric setting. The literature search revealed that RCTs only have been performed in the pediatric cardiac surgery setting.

The most updated meta-analysis[59] published in 2020 included six RCTs and one case-control study, with a total of 436 patients. It primarily investigated the effects of levosimendan on all-cause mortality in pediatric patients undergoing cardiac surgery with cardiopulmonary bypass. The authors did not find a reduction in terms of the mortality rate nor all-cause mortality in patients who received levosimendan versus other inotropes or placebo.

The authors' meta-analysis here included nine RCTs and 547 patients undergoing congenital cardiac surgery. It compared the effect of levosimendan versus placebo or other inotropes on surrogate markers of tissue perfusion being $ScvO_2$ and lactate levels that indirectly reflected the hemodynamic status of the patient. The analysis identified a significant improvement in $ScvO_2$ and a trend towards reduction of lactate levels in the postoperative period after levosimendan administration compared with the control treatment. This improvement in hemodynamic status, however, did not have a significant impact on prognostic outcome variables (longest follow-up mortality, ICU and hospital stays).

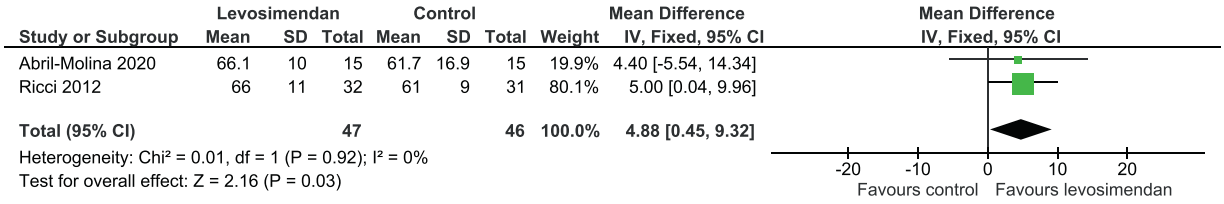

Fig. 2. A forest plot for central venous oxygen saturation ($ScvO_2$).

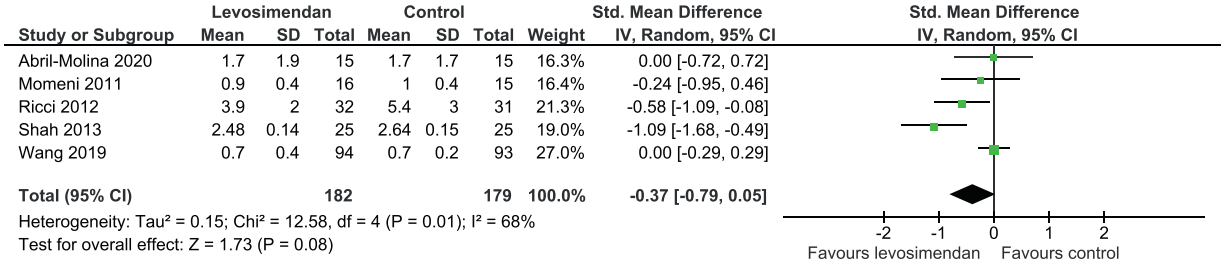

Fig. 3. A forest plot for lactate levels.

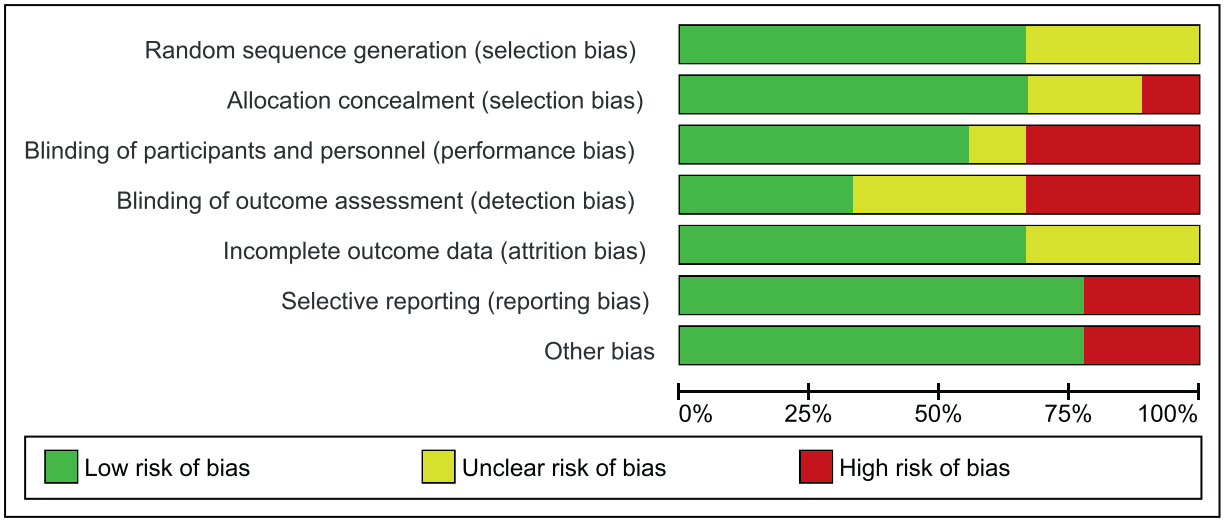

Fig. 4. Risk of bias.

Even if this systematic review and meta-analysis suggested that the use of levosimendan was not associated with major side effects in the pediatric population and that this drug may lead to greater hemodynamic improvement in this population, the authors' findings are not unbiased.

The trials selected for this meta–analysis exhibited a heterogeneous methodology. In particular, there were significant differences in levosimendan comparators, levosimendan bolus, and infusion doses, and duration of the infusions, as well as the studied endpoints. Only two studies presented $ScvO_2$ data, and only five studies presented lactate data, rendering the authors' conclusions here rather weak. Indeed, the beneficial effects of levosimendan on cardiac function cannot be shown clearly because, in children and neonates, objective measurement of cardiac output remains difficult.

Levosimendan has a unique pharmacokinetic profile, with the metabolites being more active than the mother drug; thus, allowing a prolonged inotropic effect. In neonates, plasma levosimendan was reported to be detectable for up to 14 days after the beginning of an infusion.[12] The lack of pharmacokinetic and pharmacodynamic studies in pediatric cardiac surgery also may explain the weak results obtained in this meta-analysis. In order to find a clear beneficial effect of levosimendan compared with other inotropic drugs, further studies may be needed in which the drug is administered before surgery or in which the use of much higher doses is considered before coming off cardiopulmonary bypass. Moreover, the pharmacokinetic profile of levosimendan may be different in neonates compared with children undergoing cardiac surgery.

The authors' work here showed some strengths and limitations. Their systematic review was the largest and included studies performed in all pediatric settings. However, most of the RCTs in this meta-analysis showed major bias due to a lack of blinding. Moreover, $ScvO_2$ and lactate levels only were analyzed in a few of the studies among the nine evaluated RCTs.

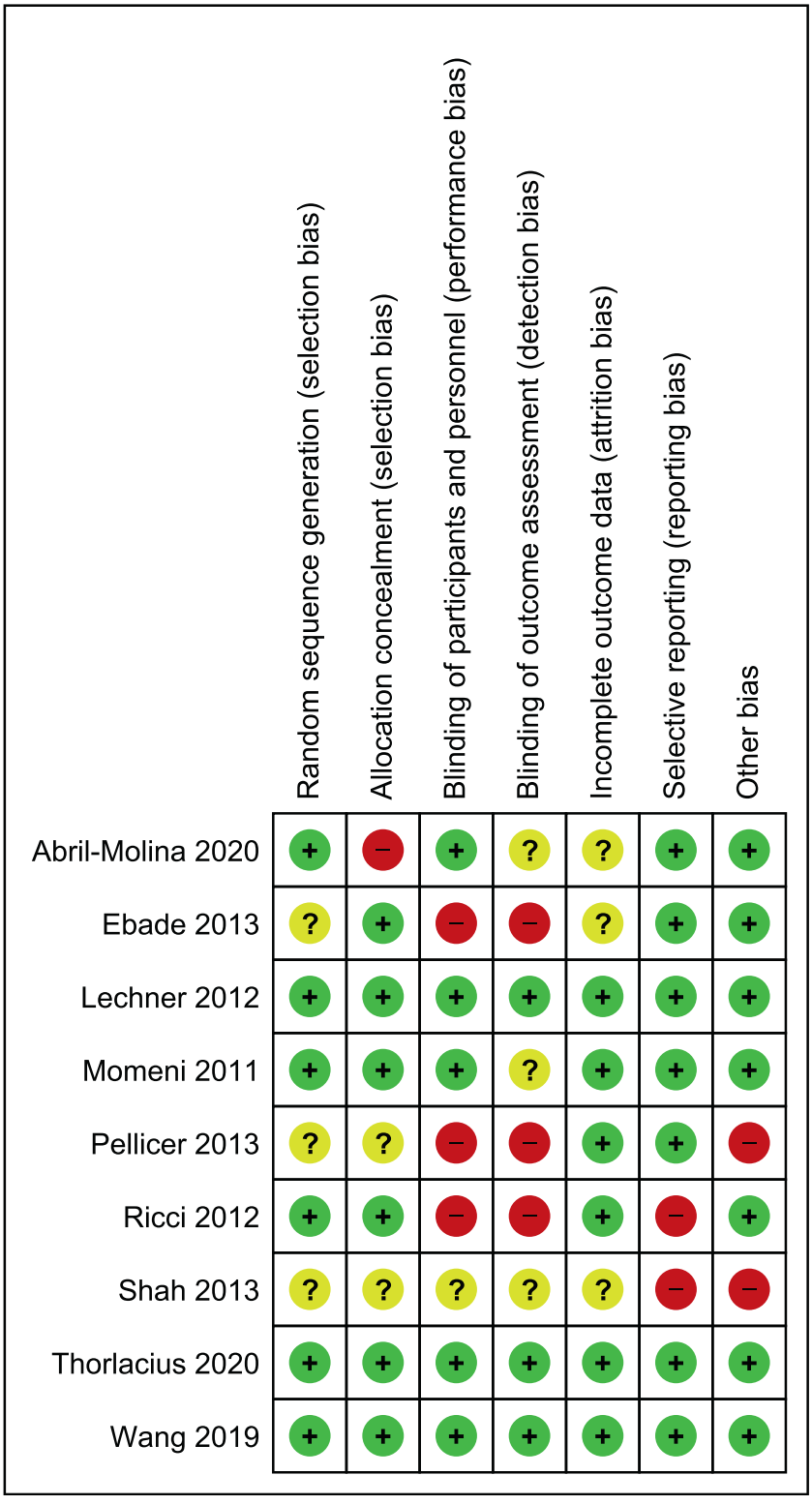

Fig. 5. Risk of bias summary.

Conclusions

This systematic review showed that levosimendan use in pediatric patients is growing and more settings are being explored. The authors' findings here suggest that levosimendan use was not associated with major side effects and may lead to hemodynamic improvement in pediatric patients undergoing cardiac surgery. Nevertheless, its effect on major clinical outcomes remains unclear. Overall, due to the lack of high-quality studies, the evidence for levosimendan

use in pediatric patients is low. Large multicenter RCTs in the pediatric setting are required to establish reductions in morbidity and mortality with the use of levosimendan.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2021.09.018.

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