Impact of More Restrictive Blood Transfusion Strategies on Clinical Outcomes: A Meta-analysis and Systematic Review

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**ABSTRACT**

**BACKGROUND:** There is accumulating evidence that restricting blood transfusions improves outcomes, with newer trials showing greater benefit from more restrictive strategies. We systematically evaluated the impact of various transfusion triggers on clinical outcomes.

**METHODS:** The Medline database was searched from 1966 to April 2013 to find randomized trials evaluating a restrictive hemoglobin transfusion trigger of <7 g/dL, compared with a more liberal trigger. Two investigators independently extracted data from the trials. Outcomes evaluated included mortality, acute coronary syndrome, pulmonary edema, infections, rebleeding, number of patients transfused, and units of blood transfused per patient. Extracted data also included information on study setting, design, participant characteristics, and risk for bias of the included trials. A secondary analysis evaluated trials using less restrictive transfusion triggers, and a systematic review of observational studies evaluated more restrictive triggers.

**RESULTS:** In the primary analysis, pooled results from 3 trials with 2364 participants showed that a restrictive hemoglobin transfusion trigger of <7 g/dL resulted in reduced in-hospital mortality (risk ratio [RR], 0.74; confidence interval [CI], 0.60-0.92), total mortality (RR, 0.80; CI, 0.65-0.98), rebleeding (RR, 0.64; CI, 0.45-0.90), acute coronary syndrome (RR, 0.44; CI, 0.22-0.89), pulmonary edema (RR, 0.48; CI, 0.33-0.72), and bacterial infections (RR, 0.86; CI, 0.73-1.00), compared with a more liberal strategy. The number needed to treat with a restrictive strategy to prevent 1 death was 33. Pooled data from randomized trials with less restrictive transfusion strategies showed no significant effect on outcomes.

**CONCLUSIONS:** In patients with critical illness or bleed, restricting blood transfusions by using a hemoglobin trigger of <7 g/dL significantly reduces cardiac events, rebleeding, bacterial infections, and total mortality. A less restrictive transfusion strategy was not effective.

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**KEYWORDS:** Clinical outcomes; Meta-analysis; Mortality; Systematic review; Transfusion

Red blood cell transfusions have been the standard of care for treating anemia for more than 100 years now, with little evidence that they improve clinical outcomes.1–3 By the early 1900s, blood transfusion was considered to be “a procedure of such simple and harmless character” that no clinical indication was needed, “the mere possibility of benefiting a condition by the addition of blood being considered sufficient warrant.”1 The practice was based on the assumption that anemia is tolerated poorly and that red blood cell transfusions improve outcomes.1,4,5 Researchers did not begin to question the evidence behind the practice until the 1980s and 1990s, when the first randomized trials were performed.6–12 By that time, the practice of blood transfusion was so ingrained in our medical framework that the approach has been to march slowly down on the transfusion trigger instead of addressing whether transfusions are beneficial at all.

The standard transfusion trigger for many years had been a hemoglobin of 10 g/dL or even higher.6,9,12,13 This arbitrary trigger has been lowered gradually to a hemoglobin...
level of 6 to 8 g/dL because studies showed that blood transfusions are associated with worse outcomes in patients with anemia due to illness or bleeding, compared with simple supportive measures such as hydration. However, a liberal transfusion practice is still common, especially for those with coronary artery disease who are thought to benefit more from blood transfusions. There have been many challenges inherent in the study of our transfusion practices, such as the broad patient base included in the analyses, the multiple indications for blood transfusions, and the confounding by indication in observational studies.

We have found no randomized clinical trials comparing transfusion with no transfusion. Instead, the available trials have compared more or less restrictive transfusion strategies using different transfusion triggers. A previous meta-analysis pooled data from randomized trials that evaluated restrictive hemoglobin transfusion triggers ranging from 7 to 10 g/dL and found that restricting transfusions significantly reduced in-hospital mortality but had no effect on other clinical outcomes. We have chosen a different approach to evaluate the available evidence. We now update the meta-analysis through April 2013 to include a subsequent trial and restrict the primary analysis to those trials with a transfusion trigger of <7 g/dL. Trials that evaluated less restrictive strategies were evaluated in a separate analysis. We also provide a systematic review of observational studies that evaluated clinical outcomes related to other more restrictive transfusion strategies.

MATERIALS AND METHODS

Data Sources and Study Selection

We conducted a comprehensive search of the MEDLINE database from 1966 to April 2013 using the terms blood transfusion and clinical trial, and scanned selected journals and references of identified articles. Studies of any language were included in the primary analysis if they were randomized controlled trials that evaluated a restrictive blood transfusion strategy using a transfusion trigger of <7 g/dL, compared with a more liberal strategy (detailed study protocol shown in Appendix Tables 1 and 2, online). We included trials of adults or children, including neonates, involving surgical or medical conditions. Trials that used a restrictive transfusion trigger trigger more than 7 g/dL were evaluated separately as a “less restrictive” strategy. Additional searches of related articles were done to perform a systematic review of the impact of various transfusion strategies.

Data Extraction and Quality Assessment

Two investigators (SS, JB) extracted data from the trials, reconciling differences by consensus. In addition, selected investigators were contacted for additional information. Clinical outcomes evaluated included in-hospital mortality, 30-day mortality, total mortality, acute coronary syndrome, pulmonary edema, bacterial infections, rebleeding, number of patients receiving any blood transfusion, and units of blood transfused per patient. Extracted data also included information on study setting, design, participant characteristics, and risk for bias for the included trials (detailed study protocol shown in Appendix, online).

Data Synthesis and Analysis

The results were reported as a risk ratio (RR) and risk difference for dichotomous outcomes, for the restrictive strategy compared with the liberal strategy, with the confidence interval (CI) set at 95% significance. For the amount of blood transfused per patient, the results were reported as a mean difference, with 95% CIs for the restrictive compared with the liberal strategy. To test for inter-study heterogeneity, the chi-square value was calculated; statistical significance was indicated by $P < .1$. The fixed-effects method was chosen to report the results because minimal heterogeneity was seen in most of the analyses. When heterogeneity was noted, the random-effects method was used. In a secondary analysis, the pooled results from trials using a less restrictive strategy were evaluated and compared with the trials in the primary analysis using the test for interaction. The analyses were performed using Review Manager, Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Role of Funding Source

The investigators received no funding for the study. No sponsor had a role in any aspect of the study, including its design and conduct, data extraction and analysis, and preparation of the manuscript.

RESULTS

Primary Meta-analysis

Search Results. The search identified approximately 4500 studies, of which 32 were potentially relevant trials evaluating transfusion triggers (Figure 1). Of these, 3 trials met inclusion criteria for the primary analysis. One
study provided unpublished information. Studies were excluded for the following reasons: Two were not randomized, 19 used a less-restrictive hemoglobin transfusion trigger of >7 g/dL, 4 did not provide a clear transfusion trigger, and 4 provided duplicate data on participants included in another trial. Of the 19 trials evaluating a less-restrictive strategy, 16 provided data on clinical outcomes and were evaluated separately.

**Trial Characteristics.** The primary analysis included 3 trials, with a total of 2364 participants followed for mean trial duration of 45 days. The characteristics of the included trials, including their risk of bias, are shown in Appendix Figure 1 (online). The mean study size was 788 participants (range, 637-889), with a mean participant age of 45.7 years (standard deviation, 16 years). Transfusion strategies were evaluated in the setting of adult critical care, pediatric critical care, and acute upper gastrointestinal bleeding.

**Data Synthesis.** The restrictive transfusion strategy was associated with a statistically significant reduction of in-hospital mortality (RR, 0.74; CI, 0.60-0.92), 30-day mortality (RR, 0.77; CI, 0.61-0.96), and total mortality (RR, 0.80; CI, 0.65-0.98), compared with the liberal strategy (Table 1, Figure 2). The risk difference for total mortality...
was −0.03 for the restrictive strategy compared with the liberal strategy (mean duration of included trials, 45 days), with a number needed to treat of 33 to save 1 life. In addition, the restrictive strategy resulted in a reduced incidence of acute coronary syndrome (RR, 0.44; CI, 0.22-0.89), pulmonary edema (RR, 0.48; CI, 0.33-0.73), rebleeding (RR, 0.64; CI, 0.45-0.90), and bacterial infections (RR, 0.86; CI, 0.73-1.00), compared with the liberal strategy (Table 1, Figure 3, Appendix, online). The results for bacterial infections were of nominal significance.

In pooled trial data, 55% of the participants in the restrictive group received a blood transfusion, compared with 94% in the liberal group (RR, 0.57; CI, 0.46-0.70 and risk difference, −0.41; CI, −0.52 to −0.29). The restrictive strategy resulted in a significant reduction in the mean number of units transfused, with a mean difference of −1.98 units (CI, −3.22 to −0.74) per patient.

No evidence for inter-study heterogeneity was found in any of the clinical outcomes analyzed (P > .25, for chi-square test). There was evidence for significant heterogeneity in the analyses of exposure to blood transfusions and the mean number of units transfused (P < .00001).

**Secondary Meta-analysis**

**Randomized Trials Using Less-Restrictive Transfusion Triggers.** Nineteen of the trials excluded from the primary analysis evaluated hemoglobin triggers of 7.5 to 10 g/dL in the restrictive strategy group, and 16 of those provided data on clinical outcomes.6-11,21,29-37 When the data from these

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials</th>
<th>Patients</th>
<th>RR or MD</th>
<th>RD</th>
<th>No. Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hospital mortality</td>
<td>2</td>
<td>1727</td>
<td>RR, 0.74 [CI, 0.60-0.92]</td>
<td>RD, −0.04 [CI, −0.04 to −0.00]</td>
<td>25</td>
</tr>
<tr>
<td>30-d mortality</td>
<td>3</td>
<td>2364</td>
<td>RR, 0.81 [CI, 0.61-0.96]</td>
<td>RD, −0.02 [CI, −0.04 to −0.00]</td>
<td>50</td>
</tr>
<tr>
<td>Total mortality</td>
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<td>2364</td>
<td>RR, 0.80 [CI, 0.65-0.98]</td>
<td>RD, −0.03 [CI, −0.05 to −0.00]</td>
<td>33</td>
</tr>
<tr>
<td>Cardiac events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>2</td>
<td>1727</td>
<td>RR, 0.44 [CI, 0.22-0.89]</td>
<td>RD, −0.02 [CI, −0.03 to −0.00]</td>
<td>50</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3</td>
<td>2364</td>
<td>RR, 0.48 [CI, 0.33-0.73]</td>
<td>RD, −0.03 [CI, −0.05 to −0.01]</td>
<td>33</td>
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<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebleeding</td>
<td>1</td>
<td>889</td>
<td>RR, 0.64 [CI, 0.45-0.90]</td>
<td>RD, −0.06 [CI, −0.10 to −0.01]</td>
<td>17</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>3</td>
<td>2364</td>
<td>RR, 0.86 [CI, 0.73-1.00]</td>
<td>RD, −0.03 [CI, −0.06 to −0.00]</td>
<td>33</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients exposed to blood</td>
<td>3</td>
<td>2364</td>
<td>RR, 0.57 [CI, 0.46-0.70]</td>
<td>RD, −0.41 [CI, −0.52 to −0.29]</td>
<td>2</td>
</tr>
<tr>
<td>Units transfused per patient</td>
<td>3</td>
<td>2364</td>
<td>MD −1.98 [CI, −3.22 to −0.74]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
trials were pooled, with a total of 4572 participants, the restrictive strategy significantly reduced the exposure to blood transfusions (RR, 0.60; CI, 0.48-0.75) and amount of blood transfused (mean difference, −0.80 units; CI, −1.24 to −0.37 units), compared with a more liberal strategy, but this had no significant effect on in-hospital mortality (RR, 0.65; CI, 0.37-1.15), total mortality (RR, 1.03; CI, 0.81-1.31), acute coronary syndrome (RR, 1.46; CI, 0.96-2.20), pulmonary edema (RR, 1.02; CI, 0.67-1.56), rebleeding (RR, 0.68; CI, 0.34-1.34), or bacterial infections (RR, 0.80; CI, 0.64-1.02).

When the pooled results for the trials from the primary analysis (hemoglobin trigger <7 g/dL) were compared with the results from the less restrictive trials (hemoglobin trigger 7.5-10 g/dL) using the test for interaction, the more restrictive strategy was associated with a greater reduction in acute coronary syndrome (P = .004), pulmonary edema (P = .002), and amount of blood transfused (P = .01), compared with the less restrictive strategy.

When all 19 trials from the primary and secondary analyses were pooled together, with a total of 6936 participants, the restrictive strategy was still associated with a significant reduction in hospital mortality (RR, 0.73; CI, 0.59-0.89), 30-day mortality (RR, 0.83; CI, 0.69-0.99), pulmonary edema (RR, 0.68; CI, 0.51-0.90), bacterial infections (RR, 0.84; CI, 0.73-0.95), and rebleeding (RR, 0.64; CI, 0.47-0.88).

**Systematic Review**

**Observational Studies Evaluating More Restrictive Transfusion Strategies.** Recent recommendations to further restrict blood transfusions have been based on studies showing the tolerability and safety of anemia under controlled normovolemic conditions, which involve the administration of fluids, oxygen, and beta-adrenergic blockers. A meta-analysis of randomized trials in the perioperative setting showed that normovolemic hemodilution, in which blood is removed and replaced with crystalloid or colloid solution, resulted in significantly less total blood loss and allogenic blood transfusions, compared with standard care. A systematic review found consistent evidence that normovolemic anemia is associated with a reduction in systemic vascular resistance and an increase in cardiac output, coronary and cerebral blood flow, and synthesis of 2,3-diphosphoglycerate in red blood cells, resulting in maintenance of oxygen delivery and extraction. Observational studies have shown that hemoglobin levels of 5 to 6 g/dL in the setting of surgery, critical illness, and acute bleeds generally are well tolerated when standard supportive measures are given, without evidence of cardiac ischemia or decrease in oxygen extraction until the hemoglobin decreases to less than 3 to 4 g/dL.

**DISCUSSION**

Pooled data from randomized controlled trials show that restricting blood transfusions to patients whose hemoglobin decreases to less than 7 g/dL results in a significant reduction in total mortality, acute coronary syndrome, pulmonary edema, rebleeding, and bacterial infection, compared with a more liberal transfusion strategy. The number needed to treat to save 1 life was 33. This strategy resulted in a 40% reduction in the number of patients receiving a blood transfusion, with an average of 2 units less per person; however, more than one half of patients still received a transfusion. In an analysis of trials that used a less restrictive strategy, with hemoglobin triggers of 7.5 to 9 g/dL, no significant reduction in morbidity or mortality was seen.
With the available evidence from observational studies, an even more restrictive transfusion strategy using a hemoglobin trigger of <6 g/dL has been recommended in some settings. Observational studies have consistently shown that transfusions are associated with an increased risk for adverse events after controlling for potential confounding variables, even when using a restrictive transfusion strategy. The increased risk seems to be directly proportional to the amount of blood transfused and the length of storage of the transfused red blood cells, and may be due to an inflammatory response to the transfused blood product. Systematic reviews also have evaluated the effect of blood transfusions on oxygen transport variables in anemic patients in the setting of surgery, critical illness, and bleed, and found no significant improvement in oxygen delivery or use compared with supportive care, despite an increase in oxygen content. This inability to improve oxygen uptake in vital organs is due to the hemodynamic response to increased blood viscosity and the loss of red cell function during preservation and storage. Conversely, there is evidence that normovolemic anemia with hemoglobin levels of 5 to 6 g/dL is well tolerated in cardiovascular or critical illness and may have beneficial hemodynamic effects.

It has been the traditional teaching that patients with cardiac ischemia should have a more liberal transfusion strategy to maintain oxygenation, but pooled observational studies on transfusion in myocardial infarction found that the rates of subsequent myocardial infarction and all-cause mortality were significantly higher in patients receiving blood transfusions compared with standard supportive measures, after adjustment for possible confounding variables. Multivariate meta-regression analysis of the pooled data revealed that the increased risk was independent of the baseline or nadir hemoglobin level. Subgroup analysis of a large critical care trial included in the primary analysis found that in patients with coronary ischemia, a transfusion trigger of <7 g/dL may be associated with improved clinical outcomes. Two small trials included in the secondary analysis evaluated a restrictive trigger of <8 g/dL in patients with symptomatic coronary artery disease; pooled results from these 2 trials showed no significant effect on cardiac events or mortality using this less restrictive strategy.

This meta-analysis found that restricting transfusions using a hemoglobin trigger of <7 g/dL reduced mortality in critical illness or bleed, with a number needed to treat of 33 to save 1 life. With millions of blood transfusions given yearly over the past century, it would be hard to calculate the hard clinical outcomes studied were unlikely to have been influenced by this. Another limitation of the study is that other patient populations, such as those with less life-threatening illnesses, were not included in the primary analysis. The objective of this study was to put together the available evidence for practicing clinicians to make sense of it all, but we are left with many unanswered questions. Unfortunately, more than one half of the patients in the restrictive group still received a blood transfusion, so we cannot directly assess the effect of transfusion versus no transfusion. At present, there are no randomized trials evaluating lower transfusion triggers, such as a hemoglobin level of 6 g/dL, which is what some of the newer guidelines recommend using on the basis of observational studies. In addition, there are no randomized trials evaluating the lower transfusion triggers in acute coronary syndrome, which at present is considered an indication for the use of a more liberal trigger. Finally, there is little information on clinical situations or nadir hemoglobin levels for which transfusions are known to improve oxygen delivery and mortality.

CONCLUSIONS
We have performed an updated meta-analysis of randomized trials that shows that a restrictive transfusion strategy using a hemoglobin transfusion trigger of <7 g/dL results in a significant reduction in acute coronary syndrome, pulmonary edema, rebleeding, infections, and total mortality, compared with a more liberal strategy. At present, there is no randomized trial evidence that blood transfusions improve oxygen delivery or clinical outcomes in any setting. More studies are needed to help guide clinicians in finding optimal treatment threshold and options in the setting of anemia and bleed.

References


APPENDIX SUPPLEMENTAL DATA

Study Protocol:
Types of studies:
We included randomized controlled trials with a concurrent control group. Trials were included if the comparison groups were assigned on the basis of a clear transfusion trigger or threshold of ≤7 g/dL, described as a hemoglobin or hematocrit level. Patients in the control group were required to receive a transfusion of red blood cells at higher hemoglobin or hematocrit thresholds than the intervention group.

Types of participants:
We included trials of patients with surgical or medical conditions, involving adults or children, including neonates.

Types of interventions:
The intervention considered was the use of red blood cell transfusion thresholds (“triggers”) as a means of providing insights for rational transfusion practices.

Outcomes assessed:
In-hospital mortality, 30-day mortality, total mortality over the period of follow-up for individual studies, acute coronary syndrome, pulmonary edema, bacterial infections, rebleeding, number of patients receiving any blood transfusion, and units of blood transfused per patient.

Search methods for identification of studies:
We did not restrict our search for trials by date, language, or publication status. A comprehensive search of the MEDLINE database from 1966 to April 2013 was conducted using the following MeSH terms and strings:

1. *Blood Transfusion/
2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp.
3. 1 or 2
4. exp Reference Standards/
5. standards.fs.
6. methods.fs.
7. 4 or 5 or 6
8. 3 and 7
9. (transfus* adj5 (polic*or practic* or protocol* or trigger* or threshold* or indicator* or stratag* or criteri* or standard*)).mp.
10. ((Red blood cell* or RBC) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or stratag* or criteri* or standard*)).mp.
11. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic*or practic* or protocol* or trigger* or threshold* or indicator* or stratag* or criteri* or standard*)).mp.
12. (transfus* adj5 (restrict* or liberal*)).mp.
13. ((blood or transfusion*) adj3 (management or program*)).mp.
14. 8 or 9 or 10 or 11 or 12 or 13
15. randomi?ed.ab.ti.
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. placebo.ab.
19. clinical trials as topic.sh.
20. randomly.ab.
21. trial.ti.
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. (animals not (humans and animals)).sh.
24. 22 not 23
25. 24 and 14.

Searching other resources:
We contacted authors of published studies for clarification of trial methodology and data. This was provided in 1 instance.21

We searched the reference lists of relevant reviews and published articles, as well as the reference lists of all included trials for further studies.

Assessment of risk of bias in included studies:
We completed a “risk of bias” table for each study, incorporating a description of the study’s performance against each of the above domains as follows: “low,” “unclear” (indicating unclear or unknown risk of bias), and “high” risk of bias.

One investigator (SC) studied the following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; other potential sources of bias.
### Appendix Figure 1
Restrictive transfusion strategy and other clinical events. CI = confidence interval.

### Appendix Table 1
Patient-Level Characteristics of Randomized Controlled Trials Evaluating a Liberal Transfusion Strategy (Hemoglobin Trigger of <7.0 g/dL) Compared with a More Liberal Strategy

<table>
<thead>
<tr>
<th>Trial Characteristics</th>
<th>Hebert et al(^{12})</th>
<th>Lacroix et al(^{28})</th>
<th>Villanueva et al(^{23*})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting</strong></td>
<td>Adult Intensive Care Unit</td>
<td>Pediatric Intensive Care Unit</td>
<td>Severe Acute Upper Gastrointestinal Bleeding</td>
</tr>
<tr>
<td><strong>Transfusion strategy</strong></td>
<td>Restrictive Arm</td>
<td>Liberal Arm</td>
<td>Restrictive Arm</td>
</tr>
<tr>
<td>Transfusion trigger (g/dL)</td>
<td>7.0</td>
<td>10.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Total (N)</td>
<td>418</td>
<td>420</td>
<td>320</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>57.1</td>
<td>58.1</td>
<td>2.98</td>
</tr>
<tr>
<td>Men (%)</td>
<td>64</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Baseline hemoglobin (g/dL)</td>
<td>8.2</td>
<td>8.2</td>
<td>8.0</td>
</tr>
<tr>
<td>Mean units of red-cell transfusion</td>
<td>2.5</td>
<td>2.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean length of storage of red cells (d [SD])</td>
<td>NR</td>
<td>NR</td>
<td>14.9 [11.8]</td>
</tr>
</tbody>
</table>

\(NR = \) not reported (in primary publication, as referenced); SD = standard deviation.
*Additional data provided by corresponding author on request.
### Appendix Table 2  
Risk of Bias Assessments for Included Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Random Sequence Generation (Selection Bias)</th>
<th>Allocation Concealment (Selection Bias)</th>
<th>Blinding of Participants and Researchers (Performance Bias)</th>
<th>Blinding of Outcome Assessment (Detection Bias)</th>
<th>Incomplete Outcome Data (Attrition Bias)</th>
<th>Selective Reporting (Reporting Bias)</th>
<th>Other Bias</th>
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</thead>
<tbody>
<tr>
<td>Hebert et al⁵²⁸</td>
<td>Low</td>
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<tr>
<td>Lacroix et al⁸</td>
<td>Low</td>
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<td>Low</td>
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<tr>
<td>Villanueva et al⁵³</td>
<td>Low</td>
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