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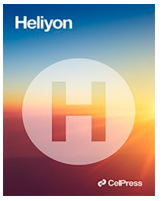

Research article

The effectiveness of cell salvage in extracorporeal circulation surgeries in relation to use of health resources after use: A systematic review and meta-analysis

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ABSTRACT

Background: Alternatives to allogeneic blood transfusions are sought for resource management reasons and it is necessary to investigate the efficiency and efficacy on Cell Salvage use. The objective of this study is to analyze the effectiveness of the Cell Salvage system in addressing factors related to healthcare service utilization that may lead to increased healthcare expenditure.
Methods: A systematic review with meta-analysis was conducted through literature search in Medline, CINAHL, Scopus, Web of Science, and Cochrane Library. Inclusion criteria were studies in English/Spanish, without year restriction and Randomized Controlled Trials design, conducted in adults.
Results: Twenty-six studies were included in the systematic review, involving a total of 4781 patients ($n_{experimental\ group} = 2365$; $n_{control\ group} = 2416$). Significant differences favored the Cell Salvage system in units of transfused Red Blood Cells, in terms of units ($p = 0.04$; SMD = −0.42 95 % CI = −0.83 to −0.02) and individuals ($p = 0.001$; RR = 0.71, 95 % CI = 0.60 to 0.84) transfused. No significant differences were found in ICU ($p = 0.93$) and hospital stay duration ($p = 0.21$), number of reoperations ($p = 0.68$), and number of units and individuals transfused in terms of platelets ($p > 0.05$).
Conclusions: Cell Salvage use holds high potential for reducing healthcare costs and indirectly contributing to improving blood and blood product reserves within blood banks. Results obtained thus far do not provide definitive evidence regarding the duration of hospital stay, ICU stay, need for reoperation, or the quantity of transfused platelets. Therefore, it is recommended to increase the number of studies to assess the impact on the economic models of the Cell Salvage system.

1. Background

The incidence and clinical burden of hemorrhagic complications in the context of cardiac surgery have been documented in

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Table 1
Table of results included.

Study (author/ year) Evidence level	Country/Design	Intervention/ Intraoperative variables and Complications	Sample (M/F)	Objectives	Implementation details	Outcomes
Bauer et al., [25] (2017) (1-)	Germany Prospective, randomised and controlled clinical trial.	CS (MiECC System©) No CS (control) CPB time: p = 0.29 Cross-clamp time: p = 0.42 Operation time: NA Complications: p > 0.05	30 (23/ 7) 36 (29/ 7)	To investigate the impact of cell washing shed blood from the operating field versus direct return to the ECC on the biomarkers for systemic inflammation.	**CS**: Suction blood was separated and CS (MiECC System©) was performed before the blood was re-transfused as an autologous RBC concentrate. **Control**: The suction blood was separated and directly re-transfused without any treatment.	The use of a CS device and processing shed blood reduces the systemic cytokine load.
Daane et al., [26] (2003) (1+)	The Netherlands Prospective randomised clinical trial	CS (Haemolite 2plus, Haemonetics Corp., Braintree, MA)] No CS (control) CPB time: p > 0.05 Cross-clamp time: p > 0.05 Operation time: NA Complications: NA	20 (11/ 9) 20 (13/ 7)	To compare the effects of the transfusion of unprocessed and cell saver-processed residual (CPB) volume on hemostasis, complement activation, postoperative blood loss and transfusion requirements after elective cardiac surgery.	**CS:** Patients in this group were transfused with processed with a blood CS (Haemolite 2plus, Haemonetics Corp., Braintree, MA)] device residual CPB volume. **Control:** Patients were transfused with unprocessed residual volume obtained from the extracorporeal circuit.	Processing CPB volume in combination with processing perioperative blood loss may result in reducing the volume of transfusion needed of allogeneic blood product.
Damgaard et al., [27] (2006) (1++)	Denmark Randomized clinical trial	CS (Autolog Medtronic, Minneapolis) No CS (control) CPB time: p = 0.39 Cross-clamp time: p = 0.19 Operation time: p = 0.39 Complications: p < 0.05* (Low cardiac output syndrome p = 0.01 No CS > CS)	30 (19/ 11) 30 (16/ 14)	To clarify the effect of using a CS intraoperatively.	**CS:** Patients in this group were transfused with processed with a blood CS (Autolog Medtronic, Minneapolis), device residual CPB volume. **Control:** Patients were transfused with unprocessed residual volume obtained from the extracorporeal circuit.	Use of CS reduced intraoperative net blood loss and seemed to reduce transfusions by 1 unit per patient, however, this was probably attributable to more complications leading to transfusion in the control group. In the future larger trials are necessary.
Damgaard et al., [28] (2010) (1+)	Denmark Randomized clinical trial	CS (Autolog CS Medtronic, Minneapolis, MN) No CS (control) CPB time: p = 0.32 Cross-clamp time: p = 0.19 Operation time: p = 0.21 Complications: p > 0.05	15 (12/ 3) 14 (11/ 3)	To investigate whether intraoperative use of a CS reduces the systemic inflammatory response after coronary operations using cardiopulmonary bypass (CPB).	**CS:** During surgery, all suctioned blood in the CS group was processed in an Autolog CS (Medtronic, Minneapolis, MN) before retransfusion; the cardiotomy suction was not used. Residual blood in the CPB circuit after the end of perfusion was also processed in the CS before retransfusion. **Control:** All suctioned blood before and after CPB was collected using the waste suction and cardiotomy suction was used during CPB.	The CS reduced the systemic levels of the proinflammatory markers IL-6 and IL-8 at 6 h after CPB. The role of the anti-inflammatory molecules IL-10 and soluble tumor necrosis factor receptors is undefined in this setting.
De vries[29] (2019) (1-)	The Netherlands Randomized clinical trial	CS versus CS plus additional WBC depletion Filter CPB time: NA Cross-clamp time: p > 0.05	189 (71/ 118) 175 (80/95	To compare conventional CS with the HemoSep© device.	**CS:** This CS (HemoSep©) device uses an approach that removes plasma and water from blood whilst retaining elements such as RBC or coagulation factors. **Control:** The CS (Sorin	In HemoSep© group PT post-operatively was shorter and aPTT was longer. In control group D-dimer and ETP levels were higher.

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Study (author/ year) Evidence level	Country/Design	Intervention/ Intraoperative variables and Complications	Sample (M/F)	Objectives	Implementation details	Outcomes
		Operation time: NA Complications: p > 0.05			Xtra) device remove white blood cells, plasma, platelets, plasma-free hemoglobin and heparin using a centrifugal process, leaving a suspension of RBC in saline for re-transfusion.	
Djaiani et al., [30] (2007) (1+)	Canada Randomized clinical trial	CS (Fresenius corporation, Concord, Calif) No CS (control) CPB time p > 0.05 Cross-clamp time: NA Operation time: NA Cross-clamp time p > 0.05	112 (100/ 12) 114 (103/9)	To determine whether the replacement of cardiotomy suction with a continuous-flow CS device would improve neuroprotection by minimizing cerebral microembolization and reduce cognitive decline in elderly patients after coronary artery bypass graft surgery.	**CS:** The continuous-flow CS was used to process shed blood before returning it back to the patient. **Control**: Cardiotomy suction was used in a standard closed venous reservoir where cardiotomy blood was collected and reinfused through the arterial circuit back to the patient.	Processing of shed blood with cell saver results in clinically significant reduction in postoperative cognitive dysfunction after cardiac surgery.
Engels et al. [31] (2016) (1++)	Netherlands Randomized prospective multicenter clinical trial	CS (Continuous AutoTransfusion System Fresenius©) No CS (control) CPB time: p = 0.76 Cross-clamp time: p = 0.33 Operation time: NA Complications: p > 0.05	99 (69/ 30) 96 (62/ 34)	To assess whether intraoperative CS may reduce lung injury following cardiac surgery by removing cytokines, neutrophilic proteases and lipids that are present in cardiotomy suction blood.	**CS**: Blood was collected from skin incision until closure of the sternum including cardiotomy suction blood and residual hearth-lung machine blood processed with a CS device. **Control**: Conventional cardiotomy suction device was used and the residual blood from the heart-lung machine was retransfused to the patient through a standard blood transfusion set.	Postoperative mechanical ventilation time, lung injury biomarkers and biomarkers of systemic inflammation were lower in CS group. Postoperative alveolar arterial oxygen gradient was not different between groups.
Goel et al., [32] (2007) (1+)	India Prospective randomized trial	CS (Dideco, Mirandola, Italy) No CS (control) CPB time: NA Cross-clamp time: NA Operation time: NA Complications: NA	24 (21/ 3) 24 (21/ 3)	To evaluate the safety and efficacy of this modality in patients undergoing off-pump coronary artery bypass grafting.	**CS**: A CS (Dideco, Mirandola, Italy) was used to salvage and autotransfuse shed blood from the time of incision. **Control**: This group was administered banked homologous packed red blood cells as the only blood replacement therapy and served as control.	The use of CS reduced the requirement for Hemoglobin transfusion. Its use is not associated with any clinically significant bleeding diathesis.
Hogan et al., [33] (2015) (1-)	United Kingdom Randomised controlled trial	CS (HemoSep©) No CS (control) CPB time: p > 0.05 Cross-clamp time: p > 0.05 Operation time: NA Complications: NA	25 (19/ 6) 28 (24/ 4)	To compare autotransfusion of residual cardiopulmonary bypass blood with residual blood concentrated using the novel HemoSep© device.	**CS**: Patients allocated CS (HemoSep©) group, blood from the bypass reservoir was drained into two treatment bags with half the volume in each. **Control**: The blood was retransfused to the patient at a rate determined by the anesthetist.	There was no difference in hemoglobin concentration in both groups. HemoSep© reduced the weight of the blood in comparison to control group.

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Study (author/ year) Evidence level	Country/Design	Intervention/ Intraoperative variables and Complications	Sample (M/F)	Objectives	Implementation details	Outcomes
Klarenbosch et al.[34] (2020) (1++)	Netherlands Multifactorial multicenter randomised trial	CS (Biofil 2, Fresenius) No CS (control) CPB time: p = 0.74 Cross-clamp time: p = 0.30 Operation time: NA Complications: p > 0.05	364 (276/ 88) 352 (256/ 96)	To assess the connection between CS and postoperative infections.	**CS**: Blood from the surgical field, cardiotomy suction blood and residual heart lung machine blood is collected. This blood is washed with a CS and retransfused. **Control**: Conventional cardiotomy suction is used and blood from the surgical field is discarded before and after heparization.	Allogenic transfusion was directly associated with infections, but CS did not. There was a positive direct effect of CS on allogenic transfusion.
Klein et al., [35] (2008) (1+)	United Kingdom Randomised controlled trial	CS (CATS–Fresenius Hemocare, France) No CS (control) CPB time: p = 0.79 Cross-clamp time: p = 0.93 Operation time: p = 0.69 Complications: p > 0.05	102 (78/24) 111 (84/27)	To determine whether routine CS for elective uncomplicated cardiac surgery reduces blood transfusion and is cost effective in the setting of a rigorous transfusion protocol and routine administration of antifibrinolytics.	**CS**: Device processed blood remaining in the CPB by the CS, which was operated by the anesthetic technicians. All recovered blood, with no minimum volume due to the design of the CS device, was transfused to the patient. **Control**: Blood aspirated from the mediastinum during surgery while the patients was heparinized was returned to the CPB reservoir. Otherwise, all blood suctioned before and after CPB was discarded. After CPB, any remaining blood in the bypass machine tubing and reservoir was collected in a bag and transfused directly to the patient.	In patients undergoing routine first-time cardiac surgery in an institution with a rigorous blood conservation program, the routine use of CS does not further reduce the proportion of patients exposed to allogeneic blood transfusion. However, patients who do not have excessive bleeding after surgery receive significantly fewer units of blood with CS.
Luque et al., [36] (2018) (1++)	Spain Analytical, prospective study with two cohorts	CS (C.A.T.S) No CS (control) CPB time: NA Cross-clamp time: NA Operation time: NA Complications: NA	162 (144/ 17) 162 (130/ 32)	To identify whether the use of the intra-uremic CS decreases the transfusional rate during the immediate postoperative period.	**CS**: An intra-surgical CS (Continuous Autologous Autotransfusion System, C.A.T.S, Fresenius) was used. **Control**: A conventional pressure suction drain was used.	The hemoglobin and hematocrit values of patients after surgery were lower in control group. The group that presented the greatest complication was the CS group, being hemoglobinuria the major complication.
Murphy et al., [37] (2004) (1++)	United Kingdom Randomised controlled trial	CS (Autolog Medtronic, Watford, UK) No CS (control) CPB time: p > 0.05 Cross-clamp time: p > 0.05 Operation time: NA Complications: p > 0.05	97 (74/ 23) 99 (86/ 13)	To compare the effects of autotransfusion of washed salvaged red cells on coagulation pathway function and blood loss after cardiac surgery in a randomized controlled trial.	**CS:** All blood loss from skin incision to commencement of CPB and then after administration of protamine to skin closure was salvaged (Autolog Medtronic, Watford, UK) at high pressure suction. All blood remaining in the CPB circuit after discontinuation of bypass was retransfused. **Control:** All blood spilt before commencement	Autotransfusion is a safe and effective method of reducing the use of homologous bank blood after routine first time coronary artery bypass grafting.

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Study (author/ year) Evidence level	Country/Design	Intervention/ Intraoperative variables and Complications	Sample (M/F)	Objectives	Implementation details	Outcomes
					of CPB and after administration of protamine was aspirated using a high-pressure sucker and discarded.	
Murphy et al., [38] (2005) (1+)	United Kingdom Randomized controlled trial	CS (Dideco, Gloucester, United Kingdom) No CS (control) CPB time: $p > 0.05$ Cross-clamp time: $p > 0.05$ Operation time: NA Complications: $p > 0.05$	30 (25/ 5) 31 (23/ 8)	To evaluate the safety and effectiveness of intraoperative CS and autotransfusion of washed salvaged red blood cells after first-time coronary artery bypass grafting performed on the beating heart.	**CS:** Patients underwent intraoperative CS (Dideco, Gloucester, United Kingdom), with autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. All blood lost, from skin incision to skin closure was salvaged at high-pressure suction, washed and auto-transfused. **Control:** All blood spilled, from skin incision to skin closure, was aspirated with a high-pressure sucker and discarded.	Intraoperative CS and autotransfusion was associated with higher postoperative hemoglobin concentrations, a modest reduction in transfusion requirements, no adverse clinical or coagulopathic effects, and no significant increase in cost compared with controls.
Niranjan et al., [39] (2006) (1+)	United Kingdom Randomized clinical trial	CS (Dideco, Gloucester, United Kingdom) CPB time: $p > 0.05$ Cross-clamp time: $p > 0.05$ Operation time: NA Complications: $p > 0.05$	20 (16/ 4) 20 (16/ 4)	To investigate the potential additive effects of autologous CS blood transfusion and CPB on blood loss, homologous blood transfusion requirements and clotting parameters in patients undergoing first time CABG.	**CS:** The device (Dideco, Gloucester, United Kingdom) was used to collect blood lost from skin incision to skin closure in the off-CPB group and from skin incision to commencement of CPB and returned to the venous reservoir. Any remaining blood in the CPB circuit after discontinuation from bypass was retransfused via the aortic cannula before decannulation. **Control:** In the off-pump group without CS all lost blood from the skin incision to closure was suctioned with a high-pressure sucker into a waste container. All blood lost from skin incision to commencement of CPB and protamine reversal to skin closure was aspirated into a waste sucker.	Off-pump CABG is associated with significant reduction in intraoperative mediastinal blood loss and homologous transfusion requirements. Autologous transfusion of salvaged washed mediastinal blood reduced homologous transfusion significantly in the on-CPB group. CS caused no significant adverse impact on coagulation parameters in on- or off-CPB CABG. Postoperative morbidity and blood loss were not affected by the use of CPB or autologous blood transfusion. We recommend the use of autologous blood transfusion in both on- and off-pump CABG surgery.
Prieto et al., [40] (2012) (1-)	Spain Randomized, prospective study	CS (C.A.T.S) No CS (control) CPB time: $p > 0.05$ Cross-clamp time: $p > 0.05$ Operation time: $p = 0.03$*(CS > No CS) Complications: $p > 0.05$	29 (21/ 8) 28 (18/ 10)	To compare the proinflammatory cytokine levels in patients undergoing cardiac surgery with and without the use of a CS.	**CS**: A CS (Continuous Autologous Autotransfusion System, C.A.T.S, Fresenius) is used throughout the procedure. At the end of surgery all remaining blood in the circuit was recovered and	High cytokine levels were observed 1 h after surgery. A higher concentration of IL-8 can be seen 24 h after surgery, concentrations of the p40 subunit of IL-12 at 1 and 24 h. In the control group, a higher

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Study (author/ year) Evidence level	Country/Design	Intervention/ Intraoperative variables and Complications	Sample (M/F)	Objectives	Implementation details	Outcomes
					concentrated by the CS and transfused to the patients. **Control**: Blood in the surgical field is aspirated using cardiotomy suction. All blood aspirated before the administration of heparin and protamine is lost.	concentration of IL-6 and p40 was observed than in CS. However, there were no significant differences in the levels of IL-1 and interferon.
Reyes et al., [41] (2010) (1-)	Spain Randomized clinical trial	CS (CATS, Fresenius Hemocare, France) No CS (control) CPB time: $p > 0.05$ Cross-clamp time: $p > 0.05$ Operation time: $p = 0.03$*(CS > No CS) Complications: $p > 0.05$	34 (24/ 10) 29 (18/ 11)	To analyze if the use of CS systems reduces the need of blood products in low-risk patients undergoing cardiac surgery.	**CS:** Device was used in the CS group (CATS, Fresenius Hemocare, France). The CS was used all along the procedure. At the end of surgery all remaining blood inside the circuits was recovered and concentrated by the CS. All recovered blood was transfused to the patients, the cardiotomy suction was used and to the patient. **Control:** All blood in the surgical field was aspirated only using the cardiotomy suction.	In low-risk patients CS system did not reduce the need of blood transfusion. Clinical outcomes were similar regardless of the use of a CS saver system. A low preoperative hemoglobin level and a low BSA were related with the use of blood products.
Scrascia et al., [42] (2012) (1-)	Italy Prospective, randomised, controlled trial	CS (Hemonetics©) No CS (control) CPB time: $p > 0.05$ Cross-clamp time: $p > 0.05$ Operation time: $p > 0.05$ Complications: $p > 0.05$	17 (8/ 9) 17 (13/ 4)	To evaluate the influence of residual pump blood salvage on inflammatory, coagulative, and fibrinolytic system activation and on postoperative hemoglobin levels and transfusion rate in patients undergoing coronary artery bypass grafting.	**CS**: CS system (Hemonetics© CellSaver©, Braintree) is used to collect residual blood remaining inside the bypass cardiopulmonary bypass at the end of the surgery. This blood is transferred into a sterile collecting bag and transfused to the patient via a standard blood-giving set at the time of skin closure. **Control**: Blood samples are collected from a peripheral arterial line after the induction of anesthesia and 24 h later. Samples are also taken from the collecting bag after the washing and concentration procedure and prior to infusion into the patient.	The recovery of blood with the use of the CS improves postoperative hemoglobin levels but induces the generation of thrombin and activation of fibrinolysis, which generates the possible appearance of coagulopathies.
Shen et al., [43] (2016) (1-)	China Randomized, prospective, controlled trial	CS (Haemonetics) No CS (control) CPB time: $p > 0.05$ Cross-clamp time: NA Operation time: $p > 0.05$ Complications: $p > 0.05$	53 (27/ 26) 50 (24/ 26)	To evaluate the impact of CS on blood coagulation in high-bleeding-risk cardiac surgery with cardiopulmonary bypass.	**CS**: Shed blood from wound and mediastina are sucked into the CS (Haemonetics, Braintree). At the end of the bypass, residual blood in the circuit is directly sucked into the reservoir. After processing, the	The heparin residual measured at the end and after the surgery were higher in CS group. The incidence of total impairment of blood coagulation at the end of surgery and after are also higher in CS group. Excessive bleeding

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Study (author/ year) Evidence level	Country/Design	Intervention/ Intraoperative variables and Complications	Sample (M/F)	Objectives	Implementation details	Outcomes
					recovered blood turned into autologous blood which is transfused back to the patient immediately. **Control**: Shed blood from wound and mediastina during the period of non-heparinization are sucked into suction device and are discarded. At the end of the bypass, residual blood in the circuit is discarded.	during postoperative was higher in CS group in comparison to the control group.
Sirvinskas et al., [44] (2005) (1-)	Lithuania Clinical trial	CS (Beckmann Coulter, Krefeld, Germany) No CS (control) CPB time: $p > 0.05$ Cross-clamp time: $p > 0.05$ Operation time: $p > 0.05$ Complications: NA	37 (29/ 8) 45 (34/ 10)	To evaluate the effectiveness of the autologous autotrans-fusion of centrifuged red blood cells from the residual blood of the CPB circuit in patients following heart surgery.	**CS group:** The group consisted of 37 patients. Who received all the residual blood remaining in the oxygenator after the CPB (collected into sterile plastic bags) during the early postoperative period. **Control:** Group consisting of 45 patients, did not receive any residual blood remaining in the oxygenator after CPB.	Autotransfusion of centrifuged red blood cells processed from the residual blood of the CPB circuit after CPB was effective in increasing HCT values 12 h postoperatively, reducing the need for donor blood product transfusions, the rate of infective complications and lenght of stay in hospital.
Sirvinskas et al., [45] (2007) (1-)	Lithuania Clinical trial	CS (Beckmann Coulter, Krefeld, Germany) No CS (control) CPB time: $p > 0.05$ Cross-clamp time: NA Operation time: NA Complications: NA	41 (27/ 14) 49 (33/ 16)	To evaluate the efficacy of collected and re-infused autologous shed mediastinal blood on a patient's postoperative course.	**CS group:** Patients received reinfusion of centrifuged autologous red blood cells processed from the shed mediastinal blood after the first four postoperative hours. The second bag was applied later and processed in a K70D Beckman Centrifuge. **Control:** Group consisting of 49 patients, all shed mediastinal blood was discarded.	Postoperative re-infusion of autologous red blood cells processed from shed mediastinal blood did not increase bleeding tendency and systemic inflammatory response and was effective in reducing the requirement for allogeneic transfusion, the rate of infective complications and the length of postoperative in-hospital stay
Tachias et al., [46] (2022) (1-)	Greece Prospective Randomized clinical trial	CS (Haemonetics Cell Saver®) No CS (control) CPB time: $p = 0.03^*$ (CS > No CS) Cross-clamp time: $p = 0.04^*$(CS > No CS) Operation time: NA Complications: NA	99 (75/ 24) 110 (87/23)	To investigate the potential effects of the centrifuged end-product on bleeding, transfusion rates, and other transfusion-related variables in adult cardiac surgery patients submitted to extracorporeal circulation.	**CS:** The device was used (Haemonetics Cell Saver®) for all patients collecting lost blood from the moment of pericardiotomy to the ECC, and after ECC weaning to the end of the surgery. The CS concentrate was transfused to the patients. **Control**: Patients underwent surgery without CS use.	Within the study's constraints, the perioperative use of the CS concentrate does not seem to affect bleeding or transfusion variables, although it could probably ameliorate postoperative oxygenation in adult cardiac surgery patients. A tendency to promote coagulation disturbances was detected.
Vermeijden et al., [47]	Netherlands Multicenter factorial	CS (C.A.T.S.) No CS (control) CPB time: $p > 0.05$	175 (140/ 35)	To investigate the effect of CS, LD filters, and their combination on	**CS group**: Cardiotomy suction blood, blood from the surgical field	There was no significant effect of CS or filter on the total number of

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Table 1 (*continued*)

Study (author/ year) Evidence level	Country/Design	Intervention/ Intraoperative variables and Complications	Sample (M/F)	Objectives	Implementation details	Outcomes
(2015) (1++)	randomized partially blinded clinical trial	Cross-clamp time: p > 0.05 Operation time: NA Complications: p > 0.05	177 (66/ 111)	transfusion requirements in cardiac surgical patients.	and residual heart lung machine blood was collected. This blood was washed in CS (Continuous Autologous Autotransfusion System, C.A.T.S, Fresenius; Haemonetics, Braintree; Sorin, Milan). **Control**: Neither CS of filter were used. Conventional cardiotomy suction device was used and blood from the surgical field was discarded after reversal of heparin.	blood products. Using a CS reduced RBC transfusions within 24 h, but not during hospital stay. Use of a CS was also significantly associated with increased transfusions of FFP and the percentage of patients who received any transfusion, but not with platelets, whereas filters did not associated significantly.
Wang et al., [48] (1994) (1-)	Taiwan Prospective clinical trial	CS (Haemonetics, Braintree, Massachusetts, U.S.A) No CS (control) CPB time: p > 0.05 Cross-clamp time: p > 0.05 Operation time: p > 0.050 Complications: NA	41 (35/ 6) 70 (54/ 16)	To assess the efficacy of this newly introduced blood conservation technique in terms of reducing postoperative transfusion requirements in two different categories of patients who underwent corrective cardiac surgical procedures.	**CS:** CS was used as the blood conservation method during surgery (Haemonetics, Braintree, Massachusetts, U.S.A). **Control**: Patients underwent surgery without CS use.	The use of CS did not increase the postoperative chest tube drainage in either the CABG or the redo patients. CS is useful in CABG patients, as far as the reduction of transfusion requirements is concerned.
Weltert et al., [49] (2013) (1+)	Italy Randomized case-control trial	CS (Haemonetics cardioPAT) CS (Haemonetics) (Control) CPB time: NA Cross-clamp time: NA Operation time: NA Complications: p < 0.05 Atrial fibrillation and Deep vein thrombosis Haemonetics > Haemonetics cardioPAT	512 (373/ 139) 537 (429/ 108)	To determine the rate of allogenic RBC usage. To evaluate the adverse events in the two distinct groups.	**CS**: Patients received both intraoperative and postoperative CS (Haemonetics cardioPAT, Braintree). Procedure consisted of sterile and continuous shed blood collection from both the operating field and the chest drains using a washing device, which allowed the reinfusion of the whole amount of saved blood. **Control**: Patients received a standard CS system (Haemonetics, Braintree) treatment of shed blood in the intraoperative phase and insertion of traditional chest drains in the postoperative time, with no CS in the last phase.	A reduction in the administration of allogeneic RBC in CS group and a lower rate of deep vein thrombosis and atrial fibrillation. A comparable 45-day mortality rate was observed.
Xie et al., [50] (2015) (1+)	China Prospective, randomized, controlled trial	CS (Haemonetics) No CS (Control) CPB time: p > 0.05 Cross-clamp time: NA Operation time: p > 0.05 Complications: NA	72 (35/ 37) 69 (29/ 40)	To evaluate the efficacy, safety and cost-effectiveness of intra-operative CS in CPB surgery.	**CS**: Shed blood from wound and mediastine were sucked into the CS (Haemonetics, USA) reservoir. At the end of the surgery, residual blood in the CPB circuit was sucked into the reservoir directly. After being filtrated, centrifugated, washed and concentrated, the recovered blood became	The proportion and quantity of perioperative allogeneic RBC transfusion were significantly lower in CS group. The incidence of residual heparin and total impairment of blood coagulation function in the 24 h after surgery, the incidence of postoperative excessive bleeding was

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Table 1 (*continued*)

Study (author/ year) Evidence level	Country/Design	Intervention/ Intraoperative variables and Complications	Sample (M/F)	Objectives	Implementation details	Outcomes
					autologous blood and was then transfused back to the patients. **Control**: Shed blood from wound and mediastina during the period of non-heparinization and residual blood were sucked into suction apparatus and were discarded.	significantly higher in CS group. Cost of allogeneic RBC transfusion and total allogeneic blood transfusion were also significantly lower in CS group, but cost of total blood transfusion was significantly higher in this group.

APTT: Activated partial thromboplastin time; BSA: Body Surface Area; CPB: Cardiopulmonary bypass; CS: Cell Salvage; ECC: Extracorporeal circulation; ETP: Endogenous thrombin potential; FFP: Fresh frozen plasma; LD: Leukocyte depletion; IAT: Intraoperative Autotransfusion; ICU: Intensive Care Unit; IL: Interleukin; MiECC System©: Minimal invasive Extracorporeal Technologies; PT: Prothrombin time; RBC: Red Blood Cell; NA: Not Available.

previous studies [3–6]. Despite the successful implementation of protocols to address the decline in hemoglobin and hematocrit levels, as well as hemorrhage, remain a common issue, particularly in multi-level surgical procedures [1,2]. Specifically, excessive post-operative bleeding was associated with prolonged mechanical ventilation after surgery, a higher likelihood of Intensive Care Unit (ICU) stay>72 h, increased workload in the ICU, and an exponential rise in total hospitalization costs (7). Postoperative bleeding was also linked to the intraoperative Cell Salvage system (specifically, the reinfusion of post-surgery Red Blood Cells (RBC), as evidenced by an elevated percentage of patients requiring allogeneic blood transfusion [8].

Hence, the scientific community is actively seeking solutions to minimize the risks associated with allogeneic blood transfusions. The utilization of a system that recovers and processes blood cells for autologous patient reinfusion raises hemoglobin and hematocrit levels without exposing them to the hazards associated with allogeneic blood transfusion [9,10]. Moreover, considering the variability in the chosen model and the management of the Cell Salvage system, it is evident that its use leads to a reduction in hospital economic costs, as there is a decrease in the expenditure on packed RBC units for transfusion [11].

Autologous blood reinfusion from the Cell Salvage system can be performed during or, more commonly, after surgery as needed [12]. Depending on the model and usage method of the Cell Salvage system, these devices essentially allow for the recovery of blood loss that occurs in the surgical field through a dual-lumen suction system. After a processing period of the retrieved blood, RBC is obtained for reinfusion back into the patient. These retrieved RBC have a hemoglobin and hematocrit concentration above 50 % [13–15].

Currently, the Cell Salvage system is employed in cardiac surgeries with extracorporeal circulation, as blood loss exceeding 200 ml is anticipated. Consequently, allogeneic blood transfusions make up more than 20 % of their utilization. Its use is particularly recommended in surgical procedures where blood loss is projected to exceed 1000 ml, in surgeries where over 20 % of patients require blood transfusions, and in emergency surgical situations [16,17].

Similarly, in situations where patients decline blood transfusions, the Cell Salvage system serves as an alternative, provided it is used continuously. Therefore, this device also benefits these types of patients. Specifically, in cases where a patient's religious beliefs prohibit blood transfusion, Cell Salvage system proves to be advantageous. The cost associated with implementing the Cell Salvage system for any type of cardiac surgery is equivalent to two units of banked packed RBC. This is why using the cell salvage system in surgeries without an anticipated blood loss>250 ml is not cost-effective, as the process would not be efficient in clinical practice [18–20].

Therefore, the objective of this systematic review with meta-analysis was to analyze the effectiveness of the cell recovery system in addressing factors related to use of health resources utilization that may lead to an increase in healthcare expenditure.

2. Methods

2.1. Search strategy and inclusion criteria

A comprehensive search was conducted across various databases, including Medline (PubMed), CINAHL, Scopus, Web of Science, and The Cochrane Library, following the recommended guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. The quality of this search was assessed using the ROB-2 tool, the details of which can be found in Table 1 [21,22]. Additionally, a search was performed on ClinicalTrials.gov, and it was verified that no similar documents were present in the PROSPERO registry. Alternative search engines were also explored to identify unconventional literature and minimize potential publication bias. Furthermore, top tier perfusionist professionals were contacted to identify any unconventional literature or

sources with potential sources of bias. The protocol for this study was registered on the PROSPERO website in July 2023 (CRD42023446583).

The following search terms were used: ("Blood retrievers" OR "Intraoperative Cell Salvage" OR "Autotransfusion System" OR "Cell Saver" OR "Operative Blood Salvage" OR "Blood Transfusion, Autologous") AND ("Cardiac Surgery" OR "Cardiopulmonary Bypass") AND ("Blood Transfusion" OR "Enhanced Recovery After Surgery" OR "Cost-Effectiveness Evaluation" OR "Hospitalization" OR Filters OR "Postoperative care" OR "Intensive Care Units" OR Reoperation OR "Blood Component Transfusion") and their equivalent in Spanish. The search equation descriptors were selected from the Medical Subject Headings (MeSH) thesaurus.

The mentioned search terms were derived from the MeSH and were applied in the search conducted between January and April 2023 by two researchers. Inclusion criteria encompassed articles published in English, Spanish and French, with no restriction on the year, related to the objectives of this study, and Randomized Clinical Trials (RCTs) conducted in adults. The exclusive selection of RCTs was carried out with the purpose of enhancing the methodological quality of the review and reducing the impact of biases in an inherently complex topic due to the diversity of factors influencing its success, such as the type of surgery, cardiopulmonary bypass time, preferences of the perfusionist assisting the surgery, patient's body surface area, and patient comorbidities, among others.

2.2. Data extraction

Ethical approval was not required to conduct this study, as it is a systematic review with a meta-analysis that does not involve patient participation. The search and selection of articles were independently conducted by two researchers (R. *C*-M and M. P–C), and in cases of disagreement, the opinion of an expert in cardiovascular surgery (M. L-O) was sought for resolution. Initially, titles and abstracts of articles were reviewed, followed by a full assessment of selected articles. Additionally, a forward and backward bibliographic search was conducted on the references cited in the selected studies. The agreement between the two researchers in assessing the suitability of the studies was quantified using the Kappa statistical test.

A data coding manual was followed to gather information from each study, including (1) author name; (2) year of publication; (3) country of origin; (4) study design; (5) sample size; (6) type of intervention (cell salvage system use versus control group); (7) participants' age; (8) study objectives; and (9) the obtained results. In addition, there are other variables that may affect health care costs related to surgical times and associated complications.

2.3. Quality and bias risk assessment

The Cochrane risk of bias assessment tool was used following Cochrane guidelines [22], which categorizes each type of risk into three levels: low, high, or uncertain. The assessed risk types included aspects such as random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, integrity of outcome data, selective reporting, and other possible sources of bias. Studies without a high risk of bias in any category were considered to have high quality (1++), while those with a high risk or three uncertain risks were rated as medium quality (1+). All other studies were considered low quality (1−).

For the risk of bias assessment, the Cochrane Handbook for Systematic Reviews of Interventions was utilized. Two independent reviewers subjectively assessed all articles and assigned ratings of "high," "low," or "uncertain" based on selection, performance, detection, attrition, and other possible biases. Disagreements were resolved through discussions to reach consensus. In case of any discrepancies between the two main researchers, the opinion of the third investigator, a specialist in perfusion (M.-L.O), was sought.

The statistical analysis and bias assessment were conducted using the Review Manager software (Revman Version 5.4®), version 5.4, developed by Cochrane Library in London, United Kingdom. Additionally, the data were imported into the GradePro® application, which aids in assessing the level of recommendation for the collected data.

2.4. Data synthesis and statistical analysis

To compare dichotomous variables, the measure of relative risk (RR) was used, accompanied by 95 % confidence intervals (CI). For continuous variables, standardized mean difference (SDM) were assessed, along with a 95 % CI. In situations where standard deviation data were not available in the study, the approach recommended by Hozo et al. [23] was applied.

Both binary and continuous data were calculated using fixed or random-effects models. The fixed-effects model was chosen initially if there was no significant heterogeneity among the studies ($I^2 \leq 50$ %). Otherwise, the random-effects model was employed [24].

Heterogeneity among the studies was assessed through chi-square tests and the I^2 test, with a statistical significance level of $p < 0.05$. I^2 values between 0 % and 25 % indicated low heterogeneity, between 25 % and 75 % moderate heterogeneity, and over 75 % high heterogeneity [24]. A forest plot was used to visualize the results of the meta-analysis, and a funnel plot was employed to assess potential publication bias among the studies. Asymmetry in the latter plot was analyzed using the funnel plot representation and evaluated with an Begg's test, considering a statistical significance level of $p < 0.05$ as indicative of evidence of publication bias. Subgroup analyses were conducted for the number of individuals transfused and the number of units transfused with respect to RBC and platelets.

Additionally, a sensitivity analysis was performed to assess the robustness of the results by sequentially omitting each study. Values of $p < 0.05$ were considered statistically significant. Sensitivity analyses were carried out by removing the most biased studies and performing different checks to assess whether they modified the results. No differences were found in the different sensitivity studies. Data from dichotomous outcomes were pooled using a random-effects model [27] to provide a more cautious estimation of the effects of Cell Salvage system use on reoperation and the number of individuals transfused with allogeneic blood or blood products. The

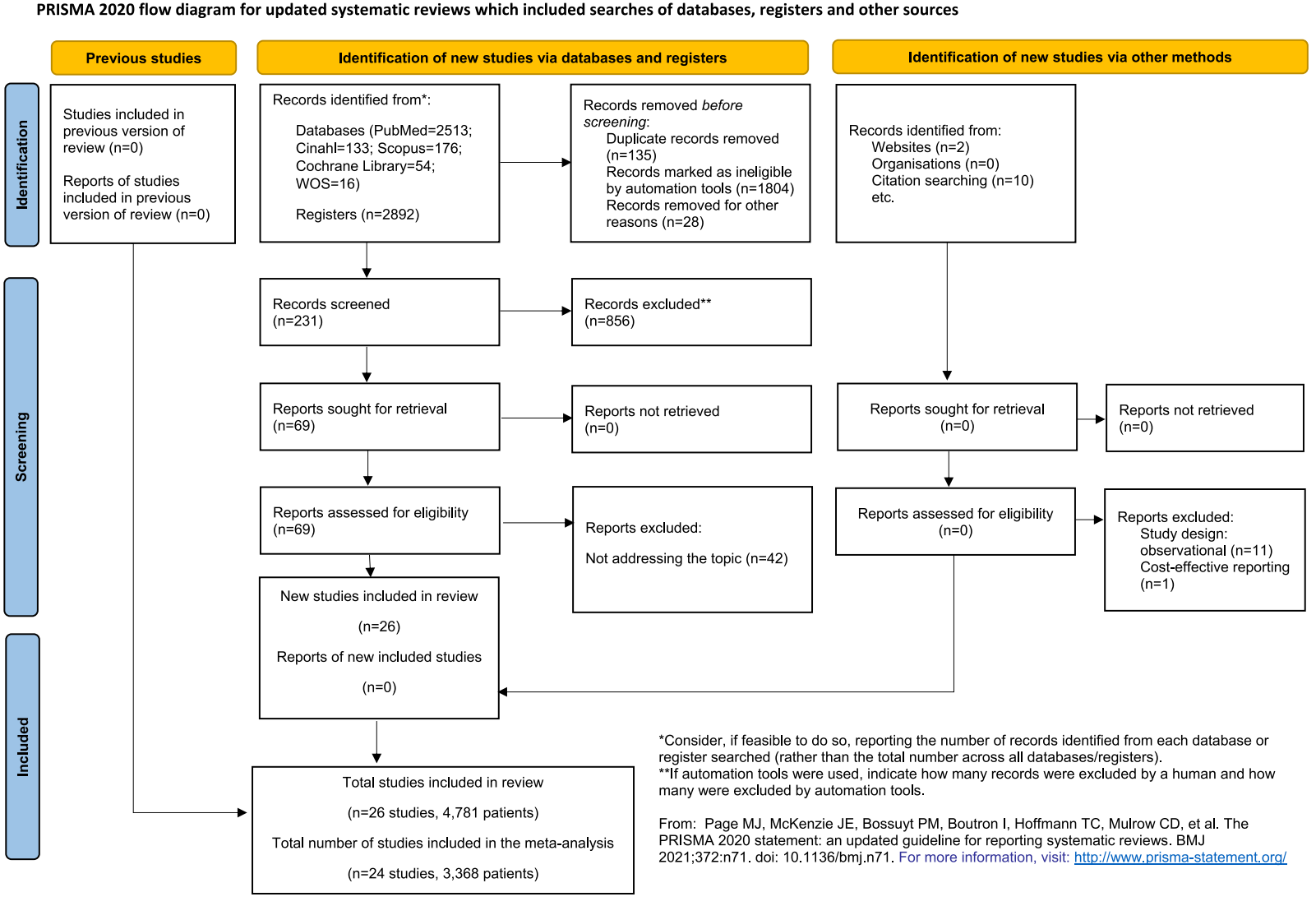

Fig. 1. PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers and other sources.

Table 2
Degree of recommendation for the use of the Cell Salvage.

Certainty assessment							N° of patients		Effect		Certainty	Outcome
N° of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Cell Salvage	Control	Relative (95 % CI)	Absolute (95 % CI)		
8	RCTs	Serious	Serious	It is not serious	It is not serious	Publication bias is strongly suspected Strong association	388	413	–	SMD **0.35** (0.03–0.67.)	⨁⨁◯◯ low	**Surgery time (hours)**
13	RCTs	Serious	Serious	It is not serious	It is not serious	Publication bias is strongly suspected Strong association	1131	1120	–	SMD **0.01** (−0.08 to 0.09.)	⨁⨁◯◯ low	**ICU stay (days)**
17	RCTs	Serious	Serious	It is not serious	It is not serious	Publication bias is strongly suspected Strong association	1339	1327	–	SMD -**0.09** (-0.23 to 0.05)	⨁⨁◯◯ low	**Hospitality stays (days)**
12	RCTs	Serious	Serious	It is not serious	It is not serious	Publication bias is strongly suspected Strong association	56/1061 (5.3 %)	51/1068 (4.8 %)	**RR 1.08** (0.75–1.54)	**4 more per 1000** (−12 to 26)	⨁⨁◯◯ low	**Reoperation**
12	RCTs	Serious	It is not serious	It is not serious	It is not serious	Publication bias is strongly suspected Strong association	288/754 (38.2 %)	403/766 (52.6 %)	**RR 0.71** (0.60–0.84)	**153 less per 1000** (−210 to −84)	⨁⨁⨁◯ Moderate	**Transfused people - RBC-transfused individuals**
8	RCTs	Serious	Serious	It is not serious	It is not serious	Publication bias is strongly suspected Strong association	68/565 (12.0 %)	62/571 (10.9 %)	**RR 1.08** (0.79–1.49)	**9 more per 1000** (-23 to 53)	⨁⨁◯◯ low	**Transfused people - Platelet-transfused individuals**
7	RCTs	Serious	Serious	It is not serious	It is not serious	Publication bias is strongly suspected Strong association	673	697	–	SMD – **0.23** (−0.33 to −0.12)	⨁⨁◯◯ low	**Units transfused - Units of RBC transfused**
4	RCTs	Serious	Serious	It is not serious	It is not serious	Publication bias is strongly suspected Strong association	530	542	–	SMD - **0.05** (-0.17 to 0.07.)	⨁⨁◯◯ low	**Units transfused - Units of platelets transfused**

The risk in the intervention group (and its 95 % confidence interval) is based on the risk assumed in the comparison group and the relative effect of the intervention (and its 95 % confidence interval). CI: Confidence Interval; RR: Risk Ratio. SMD: Standardized Mean Difference. GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the effect estimate. Moderate certainty: We are moderately confident in the effect estimate—the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited—the true effect may be substantially different from the effect estimate. Very low certainty: We have very little confidence in the effect estimate—the true effect is likely to be substantially different from the effect estimate.CI = confidence interval; RCTs = randomized controlled trial; RR = relative risk; ⨁⨁⨁◯ = level of recommendation.

effectiveness of the Cell Salvage system compared to allogeneic transfusions was expressed as RR for ICU stay in days, hospital stay in days, surgery time in minutes, number of surgical reoperations, number of individuals transfused, and number of units transfused.

3. Results

3.1. Results obtained in the article selection

A total of 2892 articles were identified in the initial search of the literature, from which no additional documents from specific clinical trial registries (Clinical Trial Gov and PROSPERO) were excluded. After eliminating 135 duplicate articles using the Zotero® reference manager, applying the inclusion criteria and evaluating the titles and abstracts of the articles, 1832 were excluded for not meeting the inclusion criteria. Finally, 69 studies were selected in the analysis for the systematic review, of which 24 offered data for meta-analysis, covering a sample of 3368 participants undergoing a cardiovascular intervention (experimental group using Cell Salvage, n = 1664; control group, n = 1704). Considering all the studies included in the systematic review, there was a total of 4781 participants. Two studies were removed from the meta-analysis because the control group was based on a different model of Cell Salvage to compare both. In the rest of the studies (n = 24 studies), the control group was encompassed by allogenic blood transfusion.

Flow diagram (Fig. 1) shows the review process. The agreement between investigators regarding the assessment of trial eligibility was excellent (Kappa statistic = 0.94).

3.2. Descriptive analysis of the found results

Of the 26 clinical trials included in the systematic review, 92 % (n = 24) were randomized, and 8 % (n = 3) did not make their randomization obvious; no crossover trials were found. Among them, three were published in 2007, and two in the years 2005, 2006, 2010, 2015, 2016, 2018. The levels of evidence assessed according to the quality of the selected articles received a score of 1++ (n = 6; 25 %), 1+(n = 9; 35 %) and 1- (n = 11; 40 %).

The topics studied were surgery time (n = 8); ICU stay (n = 13); hospitality stay (n = 17); reoperation (n = 12); RBC-transfused individuals (n = 12); platelet-transfused individuals (n = 8); platelet-transfused units (n = 4) and RBC-transfused units (n = 7). The details of each article included are provided in Table 1.

3.3. Assessment of risk of bias in selected studies and publication bias

The risk of bias was assessed using RevMan5®, represented in appendix 1 and 2 through bias assessment plots for all included studies and a summarized one-by-one plot, respectively. Allocation concealment was unclear in 45 % of cases, with approximately 25 % blinding of participants and personnel, 20 % blinding in outcome assessment, and random sequence generation below 87 %.

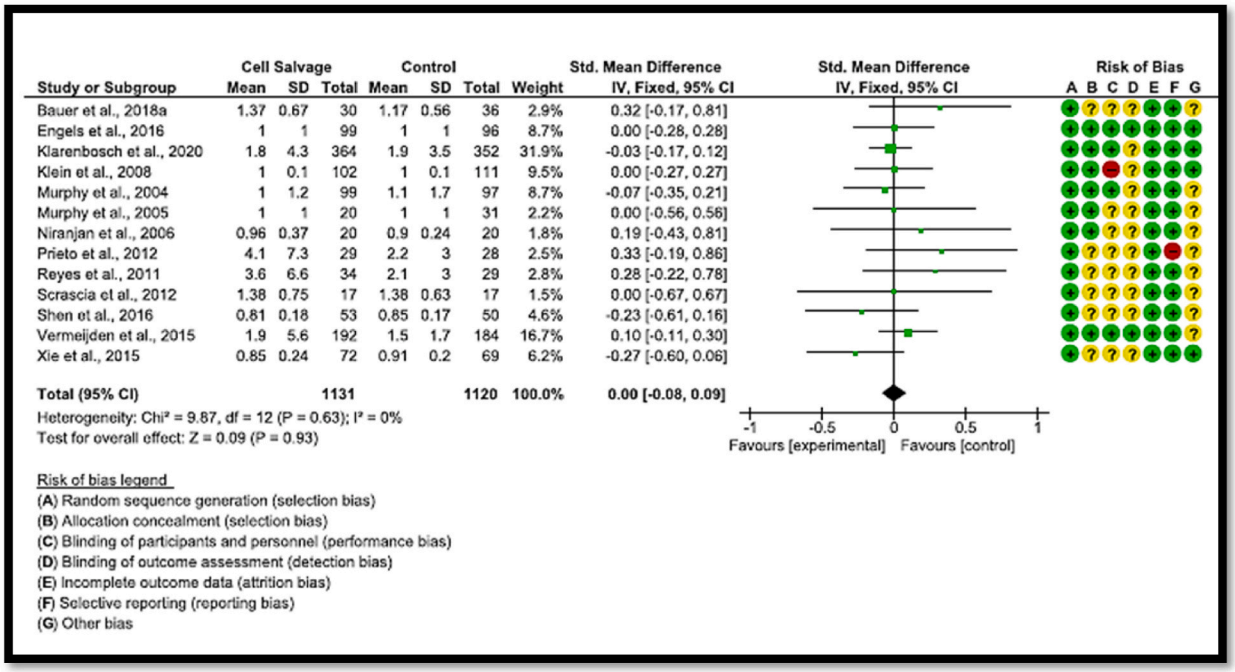

Fig. 2. Forest plot depicting Intensive Care Unit (ICU) stay after using the cell salvage system versus allogeneic transfusion.

Regarding publication bias, a funnel plot was generated for each study objective evaluated, showing an inverted funnel shape with more powerful studies concentrated in the center (Appendix 1-2).

The degree of recommendation was made through the GradePro programme after exporting the Revman results. A moderate degree of recommendation was obtained with respect to Cell Salvage in surgery time and RBC transfusions in individuals. The degree of recommendation was low for the rest of the aspects assessed (Table 2).

3.4. Results of meta-analysis

3.4.1. Efficacy of cell salvage in intensive care unit stay

In thirteen clinical trials involving 2,251participants, with 1131 in the intervention group and 1120 in the control group, the effectiveness of using the Cell Salvage in reducing ICU stay was compared with traditional transfusion-based methods. Five studies showed a high risk of bias [26,39–41,43], while eight exhibited an adequate level of quality [31,33,34,36–38,47].

A longer ICU stay was observed in the Cell Salvage group in two of the studies, whereas nine were inconclusive due to approaching the non-significance threshold, and two could not be estimated. A SMD of −0.01 was obtained; with a 95 % confidence interval of −0.08 to 0.09, and no heterogeneity was found among the studies ($I^2 = 0$ %, p = 0.63). Ultimately, no statistically significant differences were observed, both in the p-value (p = 0.93; Begg's test p = 0.07) and in the confidence interval, as it approached the no-effect line (Fig. 2).

Similarly, de Vries et al., in 2019, performed a comparison between Cell Salvage with and without filters. The results showed that the use of a filter did not increase the benefits of Cell Salvage in terms of reduced ICU days and hospitalization [29]. Along the same lines, Weltert et al. in 2003 compared Cell Salvage with the cardioPAT system®. The authors conclude that there was no difference in ICU stay (p = 0.30 Cell Salvage 2.6 SD 1.9 versus cardioPAT system® 2.4 SD 1.7). However, a reduction in hospital stay was found in favor of the cardioPAT system® (p = 0.09 Cell Salvage 7.4 SD 3.0 versus cardioPAT system ® 6.9 SD 2.1) [49].

3.4.2. Efficacy of cell salvage in length of hospital stay

In seventeen clinical trials involving 2666 participants, with 1339 in the intervention group and 1327 in the control group, the effectiveness of using the Cell Salvage in reducing hospital stay was compared. Five studies showed a high risk of bias [26,39–41,43], while one exhibited an adequate level of quality [33,34,36–38,47,50].

A longer hospital stay was observed in the Cell Salvage group in six studies, whereas this occurred in three studies in the control group. In the remaining eight studies, the results were inconclusive, approaching the no-effect threshold. A SMD of −0.09 was obtained, with a 95 % confidence interval of −0.23 to 0.05, and high heterogeneity was found among the studies ($I^2 = 74$ %, p < 0.001). Ultimately, no statistically significant differences were observed, both in the p-value (p = 0.21; Begg's test p = 0.06) and in the confidence interval, as it approached the no-effect line (Fig. 3).

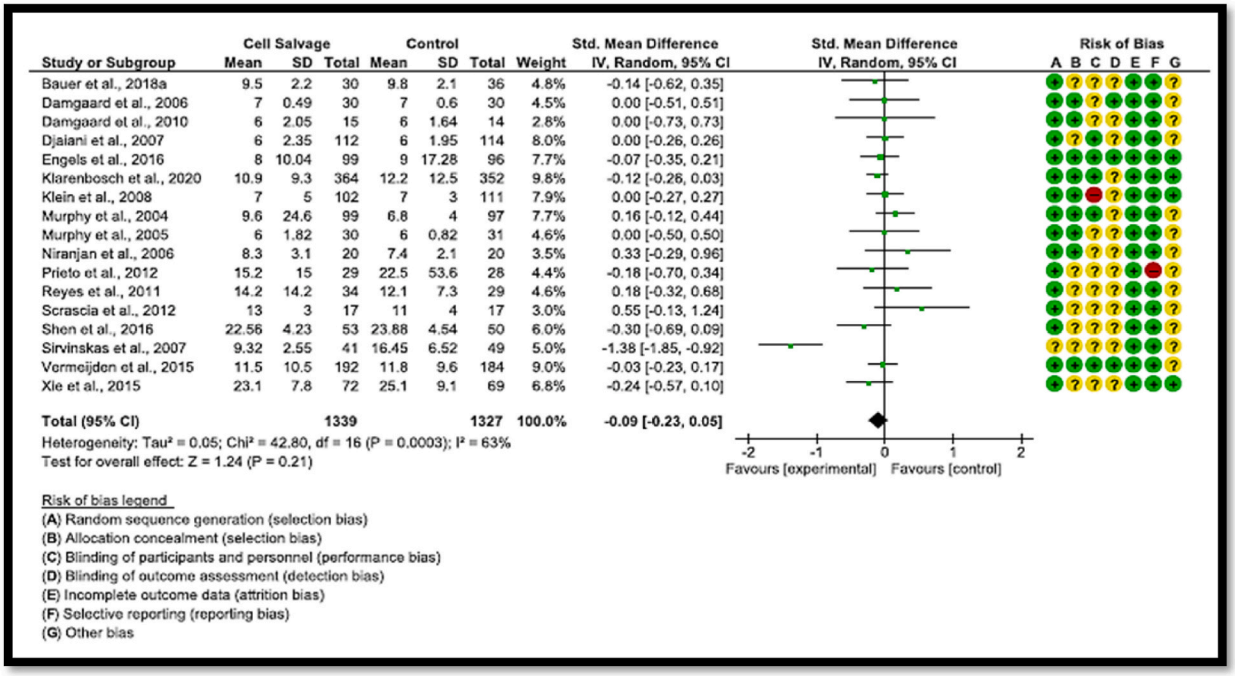

Fig. 3. Forest plot depicting hospital stay after using the cell salvage system versus allogeneic transfusion.

3.4.3. Efficacy of cell salvage in postoperative reoperation

In twelve RCTs, involving 2129 participants in both the intervention group (n = 1061) and the control group (n = 1068), the effectiveness of using the Cell Salvage was compared with the control group, where traditional methods based on allogeneic transfusion were employed. Five studies showed a high risk of bias [26,41,43,46], while one study demonstrated an adequate level of quality [29,33,34,36,47].

A higher rate of reoperation was observed in the control group (51 events) compared to the Cell Salvage group (56 events). However, no statistically significant differences were found between the two groups (RR for reoperation in the intervention group = 1.08; 95 % CI = 0.75 to 1.54), with no heterogeneity among the studies (I^2 = 0 %, p = 0.68). Ultimately, no statistically significant differences were observed, both in the p-value (p = 0.68; Begg's test p = 0.10) and in the confidence interval, as it approached the no-effect line (Fig. 4).

3.4.4. Efficacy of cell salvage in the number of individuals transfused

In twelve RCTs, with a total of 2656 participants in both the intervention group (n = 1319) and the control group (n = 1337), the effectiveness of using the Cell Salvage was compared with the control group, where traditional methods based on allogeneic transfusion were employed. Eight studies showed adequate quality [28,32,34–37,47,50]. The rest of the studies showed low quality [25,39,43,44].

For the RBC series, a total of 288 (38.20 %) transfusion cases were observed in the intervention group, while this figure rose to 403 (51.27 %) in the control group. Ten studies showed a higher number of transfused individuals in the intervention group, while the remaining two studies showed inconclusive results, with confidence intervals touching the no effect line. Statistically significant differences were found between the two groups (RR of RBC transfusion in the intervention group = 0.71, 95 % CI = 0.60 to 0.84), with moderate heterogeneity between studies (I^2 = 54 %, p < 0.05). Finally, statistically significant differences were observed, both in p-value (p < 0.001; Begg's test p = 0.09) and confidence interval, with the rhombus shifted towards the experimental group. Therefore, patients who underwent Cell Salvage received fewer RBC transfusions.

For the subgroup analysis assessing the number of individuals transfused with platelets, a total of 68 (12.04 %) cases of transfusion were observed in the intervention group, while this figure was 62 (10.86 %) events for the control group. Seven studies showed a higher number of transfused individuals in the control group, while the remaining study showed inconclusive results, with confidence intervals touching the no effect line. However, no statistically significant differences were found between the two groups (RR of platelet transfusion in the intervention group = 1.08, 95 % CI = 0.79 to 1.49). No heterogeneity was observed between the included studies (I^2 = 0 %, p = 0.92).

Finally, in RBC there is a clear trend in favor of the Cell Salvage (p < 0.001), although the moderate heterogeneity between studies should be noted (Fig. 5). On the contrary, no association was found for the transfusion of platelets (p = 0.62; Begg's test p = 0.03).

3.4.5. Efficacy of cell salvage in the number of units of RBC and platelets transfused

Seven RCTs with a total sample size of 2443 participants, considering the intervention group (n = 1203) and the control group (n =

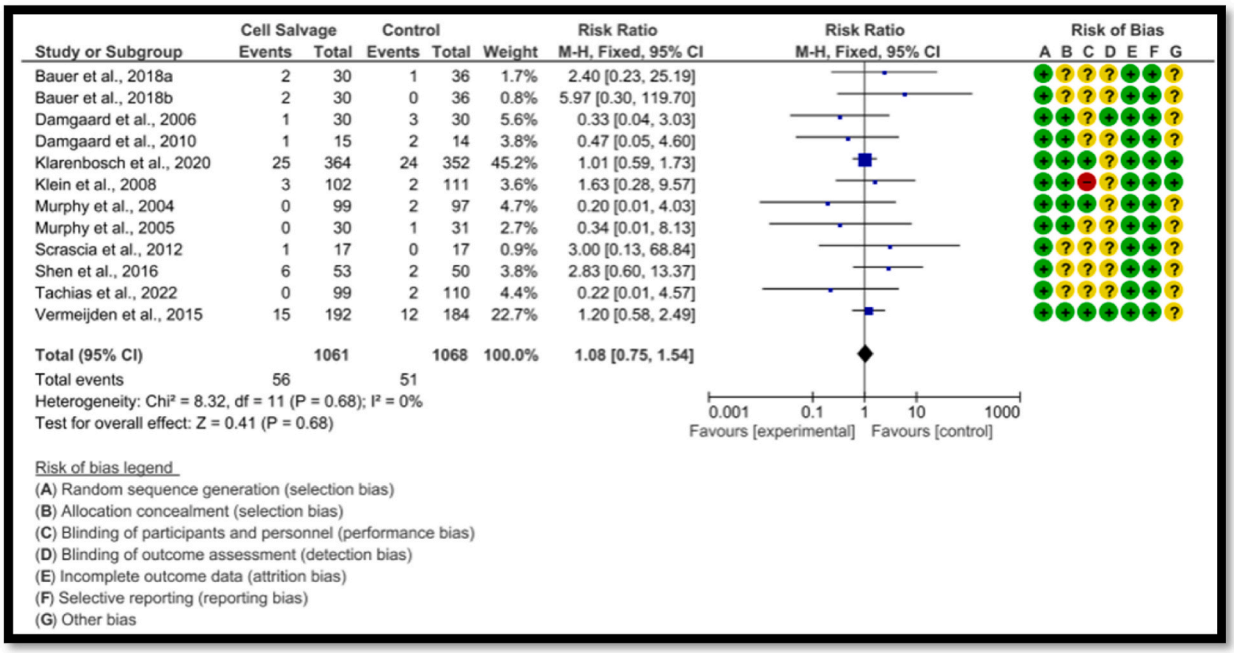

Fig. 4. Forest plot depicting reoperations after using the cell salvage system versus allogeneic transfusion.

1239), compared the efficacy of Cell Salvage use with the control group on the number of RBC units (n = 673) and platelets (n = 530). Four studies showed low risk of bias [26,32,34,50] and two studies showed medium risk of bias [43,46].

Regarding the number of RBC units transfused, in five studies there was a clear trend towards a higher number of units in the intervention group. In contrast, this was observed in one study for the control group. A SMD = −0.42 (95 % CI, −0.83 to −0.02; Begg's test p = 0.07) was obtained, with high heterogeneity between studies (I^2 = 90 %, p < 0.001). Therefore, the results show a tendency for the Cell Salvage group to be better than the transfused RBC units.

In the subgroup analysis for platelets, a higher number of units transfused in the intervention group was observed in one of the four included studies, while three were inconclusive, as it approached the no-effect threshold. A SMD = -0.10 (95 % CI, −0.33 to 0.12; Begg's test p = 0.04) was obtained, with high heterogeneity between studies (I^2 = 55 %, p < 0.08), thus no clear trend towards one of the two groups as previously.

Finally, significant differences were observed between the groups in favor of the Cell Salvage with respect to units transfused (p = 0.58, SMD = −0.30 (95 % CI = −0.54 to −0.06) (Fig. 6).

3.4.6. *Efficacy of cell salvage in surgery time*

In eight RCTs, with a total sample size of 802 participants, considering the intervention group (n = 388) and the control group (n = 413), the effectiveness of using the Cell Salvage was compared with the control group in surgery time in minutes. Four studies showed a high risk of bias [39,43,45,49], other four demonstrated an adequate level of quality [28,29,34,50].

The analysis reveals a tendency towards shorter surgery times in the control group. This statement is supported by the following data: SMD = 0.35 (95 % CI = 0.03 to 0.67), with high heterogeneity among the studies (I^2 = 78 %, p < 0.001). Ultimately, statistically significant differences are observed, both in the p-value (p < 0.05; Begg's test p = 0.06) and in the confidence interval (Fig. 7).

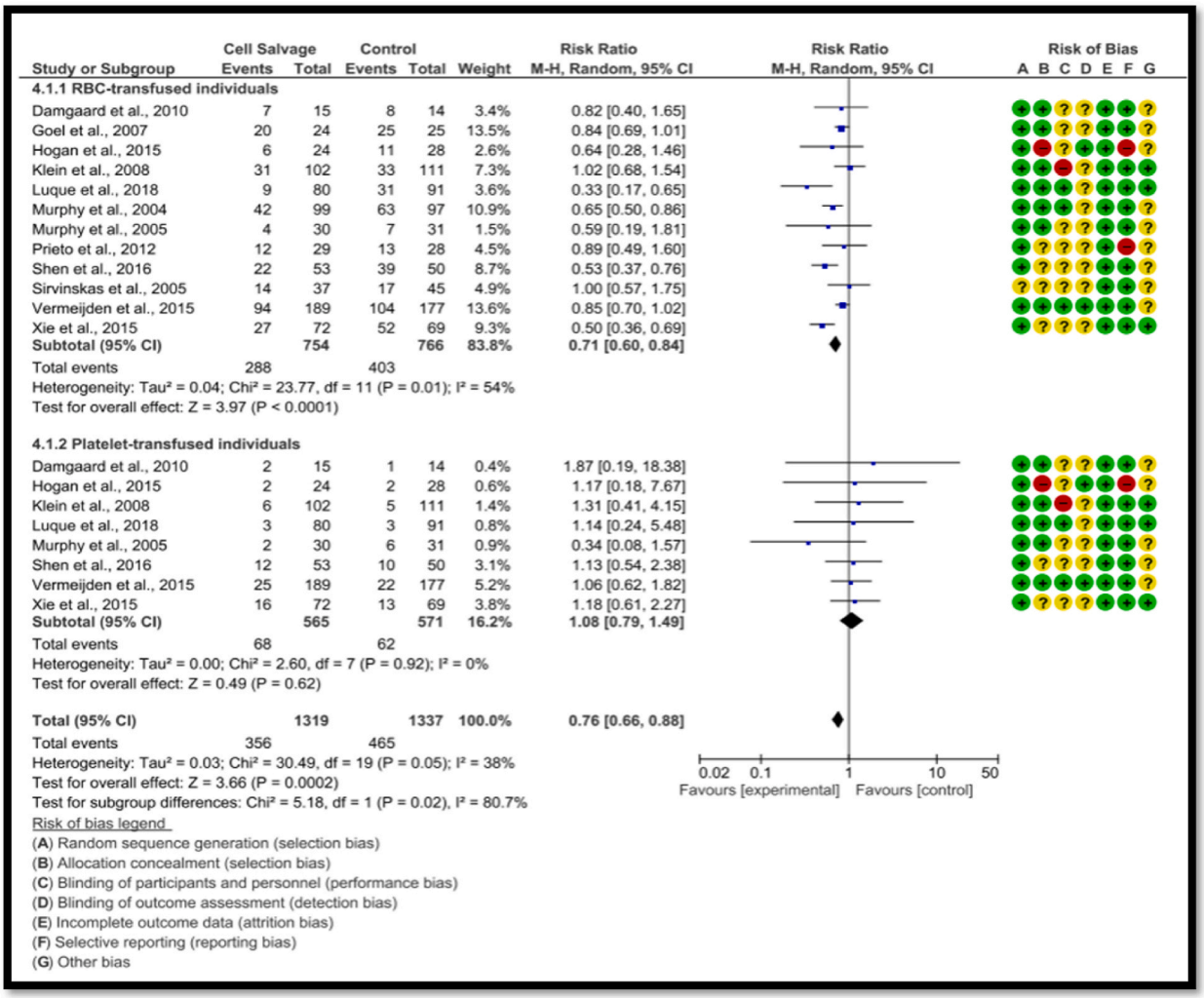

Fig. 5. Forest plot depicting the number of individuals transfused after using the cell salvage system versus allogeneic transfusion.

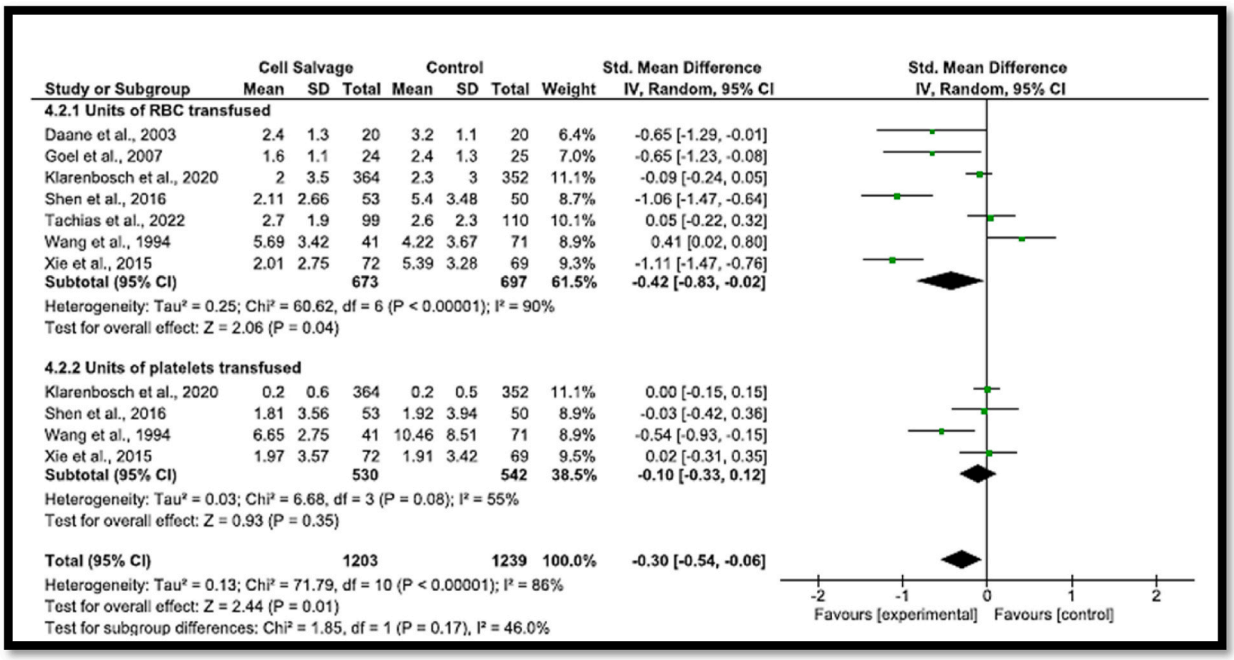

Fig. 6. Forest plot depicting the number of transfused units after using the cell salvage system versus allogeneic transfusion.

Finally, publication bias was observed in the different analyses performed. This was mitigated by an exhaustive search of the different databases and grey literature. As well as a reverse search through the references of the different studies included (Appendix 3).

4. Discussion

The objective of this systematic review with meta-analysis was to analyze the effectiveness of Cell Salvage in the utilization of factors related to the use of healthcare services that may lead to increased healthcare expenditure. It was evaluated in terms of ICU stay in days, hospital stay in days, surgery time in minutes, number of surgical reinterventions, number of individuals transfused, and number of units transfused. Most studies analyzed effectiveness in relation to ICU stay (n = 13); hospital stay (n = 17) and RBC-transfused individuals (n = 12).

This meta-analysis does not provide evidence for all potential benefits that the Cell Salvage system offers compared to allogeneic transfusions in terms of healthcare expenditure. No difference was found in ICU stay, hospitalization, re-operations and both number and units of platelets. On the contrary, only a clear improvement in the number of units of RBC transfused, as well as the number of

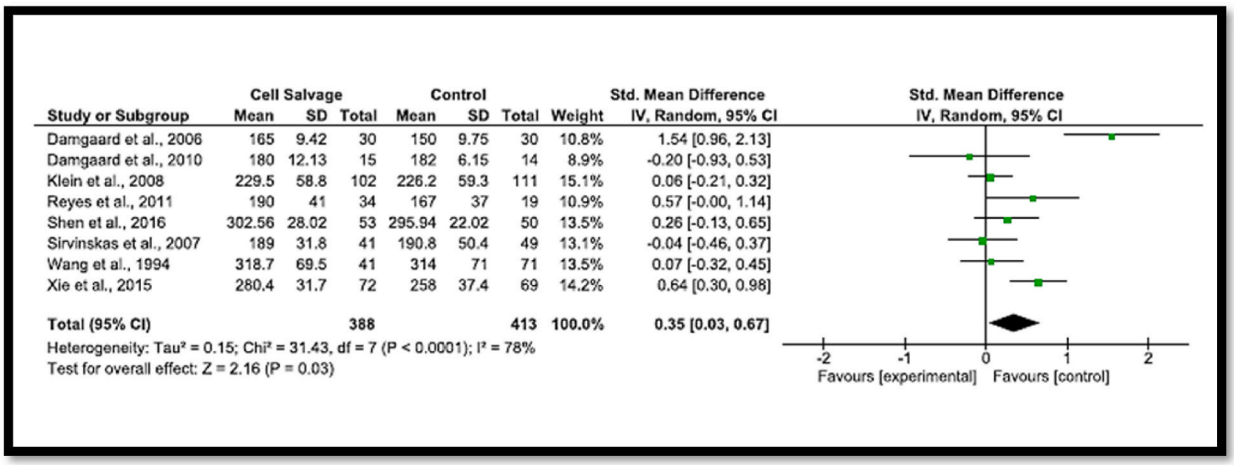

Fig. 7. Forest plot of surgery time after using cell salvage versus allogeneic transfusion.

RBC transfusions, is evident. This would translate into a reduction in the use of blood reserves from blood banks, which represents a significant healthcare expense, not only due to their preservation and transfusion but also due to the scarcity of access to blood donors, especially in certain blood groups.

This implies the need to find mechanisms capable of improving cost-effectiveness in cardiac surgery, given its high association with the need for transfusions in this population. These findings may be due to differences in the use of the Cell Salvage device, as well as the lack of protocols that unify a framework model to standardize the use of the Cell Salvage device. The different variables that can artefact the results, such as the surgeon's experience, the patient's comorbidities, the patient's surgical risk, the perfusionist's level, among others, cannot be ignored. On the other hand, the studies analyzed show homogeneity in surgical times (CPB time, cross-clamp time and operation time), surgical risk (EuroSCORE) and post-surgical complications. Encouragingly, no significant differences were found between post-surgical complications. Complications are an indirect indicator of expenditure since they can increase the length of stay in the critical care unit and hospitalization.

Finally, a benefit is found in the surgical time for patients who did not undergo Cell Salvage. This may be due to the setup time of the machine and the difficulty in its handling. Additionally, these findings may be influenced by differences in Cell Salvage usage, as well as the lack of protocols establishing a framework model to standardize its use.

The studies show a correlation between hemorrhage and healthcare costs. Al-Attar et al., in 2019, concluded that patients with hemorrhage experienced an extended hospital stay (mean incremental difference MID: 3.1 days; $p < 0.001$) and spent more days in the intensive care unit (MID: 2.4 days; $p < 0.001$). Reintervention for hemorrhage was associated with greater increases in hospital stay (MID = 4.0 days; $p = 0.002$) and days in intensive care (MID = 3.2 days; $p = 0.001$). 87 % of patients with hemorrhagic complications spent one or more days in intensive care after surgery (mean = 7.5 days, SD = 10.8), compared to 82 % of patients without hemorrhagic complications (mean = 4.0 days, SD = 5.4) [51]. In a similar vein, in previous years, Christensen MC et al., assessed that postoperative hemorrhage was associated with prolonged mechanical ventilation after surgery, a higher likelihood of staying in the ICU>72 h, a higher workload in the ICU as measured by the Therapeutic Intervention Scoring System (TISS)-28, and a mean incremental increase of € 6251 in total hospitalization costs [7].

Similarly, a study conducted in the United States, which included 8586 patients undergoing cardiac surgery between 1992 and 1995, found that reoperation due to hemorrhage was performed in 3.6 % of patients. Patients who underwent reoperation had a significantly longer hospital stay after surgery compared to those without reoperation (MID: 5.9 days) [52]. In another study, the costs associated with postoperative hemorrhage were evaluated in 122 patients (one experiencing hemorrhage and one not) who underwent cardiac surgery at a university hospital in the U.S. between 1992 and 1996. Hemorrhagic complications were associated with a mean increase of $3866 (1998 US$; US$ 7589 in 2017) in hospital costs. When patients were stratified based on the approach used to control bleeding, it was found that costs were substantially higher in patients who underwent reoperation ($9912; $19,456 in 2017 US$) compared to those treated medically (US$ 3316; $6509 in 2017) [53].

Hence, continuous updates of studies focusing on Cell Salvage usage, along with systematic reviews that consolidate the scientific evidence on this matter, become imperative. Nevertheless, the results are inconclusive depending on the aspect evaluated, and controversy exists. While several studies suggest that the use of Cell Salvage substantially reduces allogeneic blood transfusions [54–60], other authors argue the opposite [61–63]. In this regard, according to a study by Stoneham et al. [61], patients operated on using Cell Salvage had to be transfused with other allogeneic components within the first 24 h postoperatively. Similarly, Khabori et al. [62], found that the use of Cell Salvage did not decrease the transfusion rate [OR: 0.69; 95 % CI: 0.48–1.00). Continuing in the same line, the results of Zhou et al. [63], indicated that patients who underwent surgery using Cell Salvage underwent more allogeneic transfusions and had a longer stay in the ICU, resulting in higher healthcare costs.

On the other hand, Xie et al. point out that Cell Salvage is efficient and cost-effective in developed countries, but this was not the case for them, as the study was conducted in China where allogeneic transfusions are 8.9 times cheaper than in other developed countries [50]. In return, Djaiani G et al., and Weltert et al. reported that it was cost-effective if either of the following two conditions are satisfied: partial patients were with high-bleeding-risk or the quantity of intraoperative blood loss was larger than 800 ml [30,49].

Another notable aspect is that the costs of properly trained and expert personnel in the use of Cell Salvage represent a lower cost compared to the cost of an allogeneic blood unit in the blood bank [64]. These results align with the research of Davies et al. who point out that using the Cell Salvage system is cost-effective compared to other transfusion strategies, as its cost is low in relation to the cost of a blood unit [56]. However, other studies like the one conducted by Wang [58], which included thirty-one randomized clinical trials with 2282 patients, identified that using Cell Salvage to avoid allogeneic blood transfusion directly leads to an increase in FFP transfusions and, consequently, an increase in hospital costs.

In this line of inquiry, Wang, H. et al., conducted a study assessing the cost-effectiveness of Cell Salvage compared to autologous blood transfusions. To do so, they divided participants into three groups based on the amount of bleeding. Group 1 experienced losses ranging from 400 to 600 ml, Group 2 from 600 to 1000 ml, and finally, Group 3 from 1000 to 1500 ml. The authors concluded that the total cost of blood transfusion in the Cell Salvage groups was significantly higher than in the blood transfusion groups when the cost of Cell Salvage was set at 230 dollars per unit [65].

On the other hand, when the cost ranged between 199 or 184 dollars per unit, the Cell Salvage group showed a significantly higher total blood transfusion cost compared to the allogeneic transfusion group. However, this situation did not occur in Groups 2 and 3. Therefore, the authors concluded that with the reduction in Cell Salvage costs and the increase in the amount of blood lost, the cost-effectiveness of Cell Salvage has progressively improved [65]. Xie et al. [50], demonstrated that the use of Cell Salvage reduced the likelihood of patient exposure to allogeneic blood, decreased the incidence of transfusion-related diseases and reactions, but increased the total costs of transfusions. In the same vein, Attaran et al. [66], asserted that the routine use of Cell Salvage is not cost-effective.

Finally, the cohort study by Vonk et al. evaluated patients undergoing cardiac surgery without cell salvage (control; n = 531) or

with cell salvage (n = 433; Autolog, Medtronic). This study showed that the number of allogeneic red blood cell transfusions was higher in the control group (2 [1–5]) compared to the cell salvage group (1 [0–3]; $p < 0.001$). The RR for postoperative RBC transfusion was reduced to 0.76 (95 % CI = 0.70–0.83; $p < 0.001$) in the cell salvage group. In addition, patients in the cell salvage group were associated with a higher likelihood of discharge from intensive care within 24 h after surgery (RR, 1.08; 95 % CI = 1.02–1.14; p = 0.05) [67]. Along the same lines, more recent studies such as Senarslan et al. in 2022 showed that the total volume of allogeneic red blood cell transfusions ($p < 0.001$) and total blood products ($p = 0.01$) were significantly lower in Cell Salvage. The cost of red blood cell ($p < 0.001$) and total ($p = 0.03$) transfusions was lower in the Cell Salvage [68].

4.1. Limitations and strengths

This study is not without limitations. Most of the studies showed methodological biases that undermine the results. However, this limitation is mitigated by conducting a thorough review of all published scientific documentation, as well as the search for possible grey literature. The majority of the studies did not have blinding of participants or personnel, including the principal investigator. We understand that blinding operating room staff is not feasible given the physical and operational characteristics of the Cell Salvage device. In other studies, the sample size was small, which raises doubts about the study's ability to achieve adequate statistical power.

On the other hand, many studies do not describe whether a continuous or discontinuous use technique was followed, which is important information as both situations modify the patient's hemodynamic level. Additionally, they did not provide a detailed account of the technical procedure carried out in the operating room, which does not allow us to compare whether any differences found are due to a lack of standardization in Cell Salvage management. In this regard, its use is limited to the indications established by the device provider and subject to the perfusionist, who decides to use it when deemed appropriate.

The main strength of this study is to highlight the need to standardize clinical practice surrounding the Cell Salvage system in order to detect its benefits compared to the use of allogeneic transfusions. Therefore, a comprehensive search has been conducted to minimize publication bias. On the other hand, it is evident that the Cell Salvage system has great potential to reduce costs related to first-time cardiac surgery by decreasing the need for RBC transfusions.

4.2. Implications in clinical practice

Our meta-analysis, incorporating RCTs, suggests the need to establish a protocol that standardizes the criteria for action to shed light on the appropriateness of using the Cell Salvage system. Furthermore, it would be interesting in future studies to directly quantify cost-effectiveness by measuring the monetary savings in relation to indirect variables such as hospital stay, time in the ICU, reinterventions, among others. The systematic collection of transparent cost data, along with data on long-term clinical outcomes and their incorporation into future economic models, could greatly enhance the robustness of economic models regarding the cost-effectiveness of different transfusion strategies.

Many of these analyses are subject to the low quality and reliability of the data used and the use of indirect comparisons. This can affect the reliability and robustness of both clinical and economic results. Therefore, it is necessary not only to conduct more research that includes RCTs, high-quality systematic reviews, or meta-analyses with adequate statistical power, but it is also necessary to include items that directly and proportionally impact real economic costs throughout the surgical patient's process.

Under this premise, it becomes imperative to carry out studies that consider all possible items, as they are data that impact economic costs and consequently measure the effectiveness of the Cell Salvage system not only in terms of saving allogeneic blood transfusions, but also in relation to ICU stay in days, hospital stay in days, surgery time in minutes, number of surgical reinterventions, number of individuals transfused, and number of units transfused, as our review clearly demonstrates. While it is true that the Cell Salvage system is not the only variable that will determine the length of hospital stay or the number of interventions, it can be a factor to consider in mitigating bleeding and, consequently, all associated complications, including a prolongation of healthcare assistance. Similarly, there are certain unknowns surrounding Cell Salvage. It remains to be elucidated whether performance may be constrained by a lack of knowledge on the part of healthcare professionals in its use, or whether the performance of Cell Salvage is limited to certain conditions and future improvements by manufacturers. Therefore, increased utilization of evidence-based strategies for preventing and controlling bleeding may alleviate the clinical and economic burden linked with bleeding complications in cardiac surgery.

5. Conclusions

The Cell Salvage system could have significant potential to reduce healthcare costs and indirectly improve blood bank reserves. However, the findings do not provide conclusive results regarding hospital stay duration, ICU stay duration, reintervention, number and units of transfused platelets. The only advantage observed is in the number of individuals and units of RBC transfused. On the other hand, it is noted that surgical time is longer when the Cell Salvage system is used. Further studies with higher methodological rigor based on a standardized protocol are needed.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Manuel Pabón-Carrasco: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rocío Cáceres-Matos:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Salvador Martínez-Flores:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Manuel Luque-Olivero:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30459.

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