Cardiac Surgery in Jehovah's Witnesses Patients and Association With Peri-Operative Outcomes: A Systematic Review and Meta-Analysis

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Abstract: ***Background:*** **Strategies for blood conservation, coupled with a careful preoperative assessment, may be applied to Jehovah's Witnesses (JW) patients who are candidates for cardiac surgery interventions. There is a need to assess clinical outcomes and safety of bloodless surgery in JW patients undergoing cardiac surgery.** ***Methods:*** **We performed a systematic review and meta-analysis of studies comparing JW patients with controls undergoing cardiac surgery. The primary endpoint was short-term mortality**

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(in-hospital or 30-day mortality). Peri-procedural myocardial infarction, re-exploration for bleeding, pre-and postoperative Hb levels and cardiopulmonary bypass (CPB) time were also analyzed. ***Results:*** **A total of 10 studies including 2,302 patients were included. The pooled analysis showed no substantial differences in terms of short-term mortality among the two groups (OR 1.13, 95% CI 0.74-1.73, I^2=0%). There were no differences in peri-operative outcomes among JW patients and controls (OR 0.97, 95% CI 0.39-2.41, I^2=18% for myocardial infarction; OR 0.80, 95% CI 0.51-1.25, I^2=0% for re-exploration for bleeding). JW patients had a higher level of preoperative Hb (Standardized Mean Difference [SMD] 0.32, 95% CI 0.06-0.57) and a trend toward a higher level of postoperative Hb (SMD 0.44, 95% CI -0.01-0.90). A slightly lower CPB time emerged in JWs compared with controls (SMD -0.11, 95% CI -0.30-0.07).** ***Conclusions:*** **JW patients undergoing cardiac surgery, with avoidance of blood transfusions, did not have substantially different peri-operative outcomes compared with controls, with specific reference to mortality, myocardial infarction, and re-exploration for bleeding. Our results support the safety and feasibility of bloodless cardiac surgery, applying patient blood management strategies. (Curr Probl Cardiol 2023;48:101789.)**

Introduction

Given the refusal of blood transfusion, major surgery in Jehovah's Witnesses (JW) patients represents a major challenge in clinical practice requiring dedicated and experienced surgical teams.[1,2] Previous studies have shown that blood conservation strategies together with a careful preoperative assessment of patients at higher risk of bleeding complications can be applied to JW patients achieving favorable clinical outcomes at short and long-term follow-up.[3-5] Bloodless cardiac surgery has been proposed as a valid and safe alternative in this specific and high-risk subgroup of patients laying the ground for a wider application in clinical practice and clinical reports based on a relatively small series of JW patients have been reported.[6,7]

An updated analysis of available data is needed to appropriately assess clinical outcomes and the safety of bloodless surgery in JW patients undergoing cardiac surgery. Accordingly, we performed a systematic review and meta-analysis with the aim to analyze peri-operative outcomes and short-term mortality in this unique subset of patients compared to controls.

Methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations (http://www.prisma-statement.org).

Search Strategy and Study Selection

A systematic and comprehensive literature search was performed on multiple electronic databases (PubMed, Scopus and Web of Science) from inception to October 31, 2022. The following terms were used in combination: "Jehovah's Witnesses", "Jehovah", "Witnesses" and "surgery", "cardiac surgery". Previous reviews on this topic were also assessed to identify any other potential publications to include in the present work. No language restriction was applied.

The inclusion criteria were: (i) two cohorts of patients, one of JW patients and one of controls that underwent cardiac surgery; (ii) studies published after 2005; (iii) sample size of at least 50 patients overall. We excluded studies on highly selected cohorts of patients (i.e., studies that enrolled only anaemic patients), articles not in English, conference abstracts, letters, comments, editorials, case reports, systematic reviews, and meta-analysis. In the case of two or more studies based on the same cohort of patients, we selected the study with the highest number of patients included or the most recently published one.

All titles and abstracts retrieved from the literature search have been independently screened by two authors (D.A.M. and N.B.). After the first screening phase, the remaining articles were then evaluated according to full-text eligibility. Disagreements were resolved by collegial discussion including a third senior author (G.B.).

Data Extraction

Two authors (D.A.M. and N.B.) independently extracted data from the studies included through a standardized electronic form. We extracted data on sample size, number of patients, the proportion of females and type of intervention (coronary artery bypass graft [CABG], valvular heart

surgery or combined). We extracted data regarding the following outcomes: short-term mortality (defined as in-hospital death or within 30 days from intervention), peri-procedural myocardial infarction; re-exploration for bleeding. We also extracted data regarding haemoglobin (Hb) levels before and after the intervention and cardiopulmonary bypass (CPB) time.

Outcomes Definition

The primary endpoint of our study was to compare short-term mortality (in-hospital or 30-day mortality) among JW patients and controls.

In addition, we also compared the two groups for: (i) peri-procedural myocardial infarction; (ii) re-exploration for bleeding; (iii) preoperative Hb levels; (iv) postoperative Hb levels and (v) CPB time. Each outcome was defined as per the original included studies.

Quality Assessment

Two authors (P.C and M.M.) independently evaluated all studies to assess the risk of bias. We evaluated the risk of bias using a customized tool based on the Newcastle−Ottawa Scale (NOS) for cohort studies composed of 8 items across three domains (Selection, Comparability, Outcome) (Table S1). Studies with a NOS < 5 were categorized as at high risk of bias. Disagreements were resolved by collegial discussion with a third senior author (G.B.).

Statistical Analysis

Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were reported as counts and percentages.

For the two groups, the number of events was compared using random-effect models. For continuous outcomes, mean and standard deviation (SD) were compared with the inverse variance method. Pooled estimates were reported as Odds Ratio (OR) and 95% confidence interval (CI) for risk ratios or comparable estimates, or as standardized mean difference (SMD) and 95% CI for continuous variables. We also computed 95% prediction intervals (PI), that provide helpful information on the variability and heterogeneity of the estimate. Tau2 was estimated using the Restricted Maximum Likelihood method.

The inconsistency index (I^2) was used to measure heterogeneity. According to prespecified cut-offs, low heterogeneity was defined as an $I^2 < 25\%$, moderate heterogeneity as an I^2 between 25% and 75%, and

high heterogeneity as an $I^2 > 75\%$. For those outcomes with an $I^2 > 50\%$ we performed a sensitivity analysis with a 'leave-one-out' approach, in which all studies are removed one at a time to analyze their influence on pooled estimate and heterogeneity.

We evaluated possible publication bias for study outcomes through visual inspection of funnel plots. All the statistical analyses were performed using R version 4.2.2 (The R Foundation, 2022), using the 'dmetar' package.

Results

The systematic literature search identified a total of 1,015 records. Of these, 954 were excluded after duplicate removal and based on title/abstract screening. A total of 61 full-text articles were further evaluated for eligibility, and 10 studies[8-17] were included in the final analysis (Fig. 1).

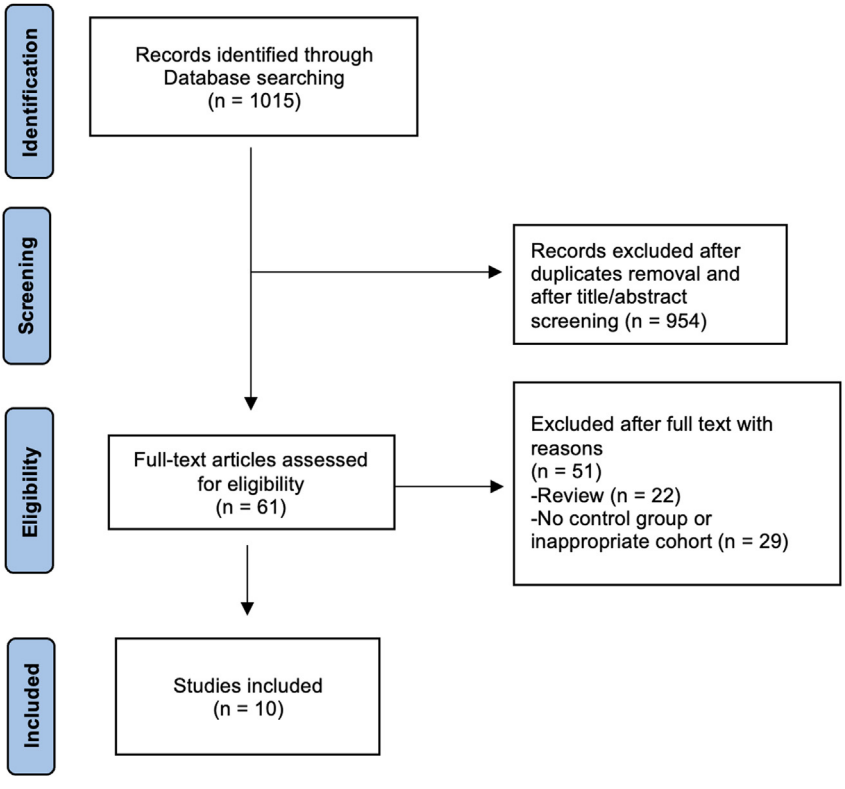

FIG. 1. Flow diagram showing the study selection process.

Study and Patients' Characteristics

The main characteristics of the 10 included studies are shown in Table 1. Overall, a total of 2,302 patients were included in these studies (950 JWs vs 1352 matched controls). All the studies were retrospective.[8-17]

Study years ranged from 1983 to 2021. None of the JW patients included in the studies received blood transfusions during the peri-operative period. Patients included underwent various types of cardiac interventions, including CABG surgery, valvular heart surgery or aortic surgery (alone or in combination). The strategies that were adopted for preparing JW patients and possibly control patients for blood-less cardiac surgery interventions, are shown in Table 2.

Mortality, Myocardial Infarction, and Re-Exploration for Bleeding

All the 10 studies included reported data on in-hospital/30-day mortality in the two groups (JW patients and controls, respectively). The pooled analysis showed no substantial differences in terms of short-term mortality among the two groups (OR 1.13, 95% CI 0.74-1.73, I^2=0%) (Fig. 2, Panel A). Data on myocardial infarction rates and the need for surgical re-exploration for bleeding were reported in 9 studies.[8-16] There were no meaningful differences for these outcomes between JW patients and controls (OR 0.97, 95% CI 0.39-2.41, I^2=18% for myocardial infarction; OR 0.80, 95% CI 0.51-1.25, I^2=0% for re-exploration for bleeding) (Fig. 2, Panel B and Panel C).

Peri-Operative Haemoglobin Levels and Cardio-Pulmonary Bypass Times

A total of six studies[8,11-14,17] reported preoperative Hb levels, while five studies[8,11-14] reported data on postoperative Hb levels. As shown in Fig. 3 (Panel A and Panel B), we found that JWs patients had a higher level of preoperative Hb (SMD 0.32, 95% CI 0.06-0.57) and postoperative Hb as well (SMD 0.44, 95% CI -0.01-0.90). The sensitivity analysis with the leave-one-out approach showed that the study by Nanni et al.[13] was the most important contributor to heterogeneity (Fig. S2 and S3). Finally, a slightly lower CPB time emerged in JWs compared with controls (SMD -0.11, 95% CI -0.30-0.07) across six studies[8,9,11-14] (Fig. 3, Panel C).

TABLE 1. Main characteristics of the studies included.

Study	Year	Type	PS	Group	N	Age[†]	Female	Type of cardiac surgery			Pre-operative Hb	Post-operative Hb	Trasfusion	Endpoints	Main findings
								Bypass	Valve	Combine					
Nanni et al. 2022[13]	2016-2021	R	No	C JW	113 113	70 (61-76) 71 (61-76)	38 (33.7) 39 (34.5)	27 (23.9) 28 (24.8)	64 (56.6) 63 (55.7)	12 (10.6) 12 (10.6)	13.9±1.6 14.0±1.4	10.8±1.2 10.8±1.8	56 (49.6) 0 (0.0)	Composite of in-hospital perioperative adverse events and all-cause mortality	No differences between groups -Composite outcome: aOR 0.91, 95% CI 0.54-1.57 -All-cause mortality: aHR 0.77, 95% CI 0.24-2.42
Willcox et al. 2020[15]	2007-2018	R	Yes	C JW	118 118	60 (60-76) 68 (59-75)	50 (42.4) 37 (31.4)	55 (46.6) 59 (50.0)	29 (24.6) 25 (21.2)	17 (14.4) 17 (14.4)	13.2 (12.0-14.5) 13.5 (12.2-14.6)	8.5 (7.5-9.5) 9 (7.9-9.9)	49% 0 (0.0)	Incidence of AKI In-hospital mortality	-Lower AKI in pts refusing transfusion (4% vs 8%) -No difference for in-hospital mortality (2% vs 3%)
Muller et al. 2020[11]	2008-2017	R	Yes	C JW	35 35	68±13 68±9	14 (40.0) 14 (40.0)	16 (45.7) 16 (45.7)	15 (42.9) 15 (42.9)	2 (5.7) 2 (5.7)	13.2±2.0 14.1±1.1	10.3±1.3 11.5±1.5	18 (51.4) 0 (0.0)	In-hospital and long-term mortality	No differences between groups -In-hospital mortality: 2.9% in each group - Survival probability at 5 years: (JWs vs no-JWs): 77.6% vs 73.6%
Reyes et al. 2018[12]	1988-2013	R	No	C JW	172 172	62±11 61±11	88 (51.2) 88 (51.2)	29 (16.8) 29 (16.9)	121 (70.3) 121 (70.3)	19 (11.0) 19 (11.0)	13.1±2.0 13.9±1.3	10.8±1.8 11.8±1.6	83 (48.2) 0 (0.0)	30-days and operative mortality	-30-day mortality higher in JWs (9.9% vs 3.5%) -Similar operative mortality (9.9% vs 7.6%)

(*continued on next page*)

TABLE 1. (*continued*)

Study	Year	Type	PS	Group	N	Age†	Female	Type of cardiac surgery			Pre-operative Hb	Post-operative Hb	Trasfusion	Endpoints	Main findings
								Bypass	Valve	Combine					
Valle et al. 2017[16]	2008-2016	R	No	C	48	63±11	16 (33.3)	28 (58.3)	12 (25.0)	1 (2.1)	12.7 (11.1-14.2)	9.4 (8.8-10.9)	NR	In-hospital mortality	Higher rate in JWs (18% vs 4.2%)
				JW	16	61±12	7 (43.7)	7 (43.7)	7 (43.7)	2 (12.5)	13.6 (11.7-14.2)	9.2 (7.5-11.6)	NR		
Marinakis et al. 2016[14]	1991-2007	R	No	C	62	62±14	20 (32.3)	48 (48.5)	18 (29.0)	6 (9.7)	13.7±1.7	10.4±1.3	17 (27.4)	In-hospital mortality	Similar in the two groups (3% vs 2%)
				JW	31	62±15	10 (32.3)	15 (48.4)	9 (29.0)	3 (9.7)	14.2±1.6	10.6±1.8	0 (0.0)		
Guinn et al. 2015[17]	2005-2012	R	No	C	90	64 (58-72)	43 (47.8)	46 (51.1)	36 (40.0)	8 (8.9)	12.9±1.4	NR	61 (67.8)	Difference in costs JW and controls and 30-day mortality	No difference shown in total cost from day of surgery to discharge between the two groups ($35,306 for controls vs. $31,152 JWs) 30-day mortality was zero in both groups
				JW	45	65 (58-72)	22 (48.9)	23 (51.1)	18 (40.0)	4 (8.9)	12.9±1.4	NR	0 (0.0)		
Pattakos et al. 2012[9]	1983-2011	R	Yes	C	322	61±14	134 (41.6)	NR	NR	NR	NR	NR	322 (100)	Post-operative morbidity complications, in-hospital mortality, and long-term survival	JWs and controls similar 20-year survival (34%, 95% CI 31%-38%; vs 32%, 95% CI 28%-35%) Similar risks of in-hospital mortality. JWs had fewer MI, postoperative ventilator support, additional operations for bleeding, shorter intensive care unit and postoperative lengths of stay.
				JW	322	62±13	134 (41.6)	NR	NR	NR	NR	NR	0 (0.0)		

(*continued on next page*)

TABLE 1. (*continued*)

Study	Year	Type	PS	Group	N	Age†	Female	Type of cardiac surgery			Pre-operative Hb	Post-operative Hb	Trasfusion	Endpoints	Main findings
								Bypass	Valve	Combine					
Bhaskar et al. 2010[8]	2002-2005	R	Yes	C JW	196 49	61±12 65±10	82 (41.8) 21 (42.9)	121 (61.7) 25 (51.0)	51 (26.0) 13 (26.5)	24 (12.2) 11 (22.4)	12.8±1.6 13.7±1.7	9.9±1.2 10.8±1.5	196 (100) 0 (0.0)	Operative mortality	No differences between groups (aOR 0.62, 95%CI 0.12-3.50)
Stamou et al. 2006[10]	1990-2004	R	Yes	C JW	196 49	60±15 62±9	79 (40.3) 22 (44.9)	122 (62.2) 38 (77.6)	13 (13.3) 3 (6.1)	6 (3.1) 2 (4.1)	NR NR	NR NR	196 (100) 0 (0.0)	Operative mortality	No differences between groups (OR 0.66, 95% CI 0.12-3.59)

†Results are reported as mean ± SD or as median (IQR). AKI, acute kidney injury; C, control; CC, case control; CI, confidence interval; Hb, hemoglobin; HR, Hazard Ratio; JW, Jehovah's witnesses; NR, not reported; PS: propensity score OR, Odds Ratio; R, retrospective

TABLE 2. Peri-operative blood management in JW patients and controls

Study	
Nanni et al., 2022	- Pre-operative EPO or Intravenous iron when indicated* - Cell salvage protocol**
Willcox et al., 2020	- Intraoperative tranexamic acid** - Cell salvage protocol**
Muller et al., 2020	- Pre-operative EPO or Intravenous iron when indicated* - Intraoperative tranexamic acid* - Cell salvage protocol* - Post-operative EPO or Intravenous iron when indicated*
Reyes et al., 2018	- Pre-operative EPO or Intravenous iron when indicated* - Intraoperative Aprotinine** - Cell salvage protocol**
Valle et al., 2017	- Pre-operative EPO when indicated*
Marinakis et al., 2016	- Pre-operative EPO when indicated* - Intraoperative aprotinin or tranexamic acid** - Cell salvage protocol*
Guinn et al., 2015	- Pre-operative EPO or Intravenous iron when indicated* - Intraoperative Aprotinin* - Cell salvage protocol*
Pattakos et al., 2012	- Not reported
Bashkar et al., 2010	- Pre-operative EPO or Intravenous iron when indicated* - Intraoperative tranexamic acid* - Cell salvage protocol * - Post-operative EPO or Intravenous iron when indicated*
Stamou et al., 2006	- Cell salvage protocol*

*Only for JW patients.
**Both groups of patients.

Quality Assessment and Publication Bias

The Newcastle-Ottawa scale was used for the quality assessment of the studies. All the studies had a score ≥5, suggesting a satisfactory quality in terms of the selection of the population and comparability of the groups.[8-17] The funnel plots for all the outcomes analyzed did not show substantial asymmetry suggesting publication bias (Fig. S1, Panels A-F).

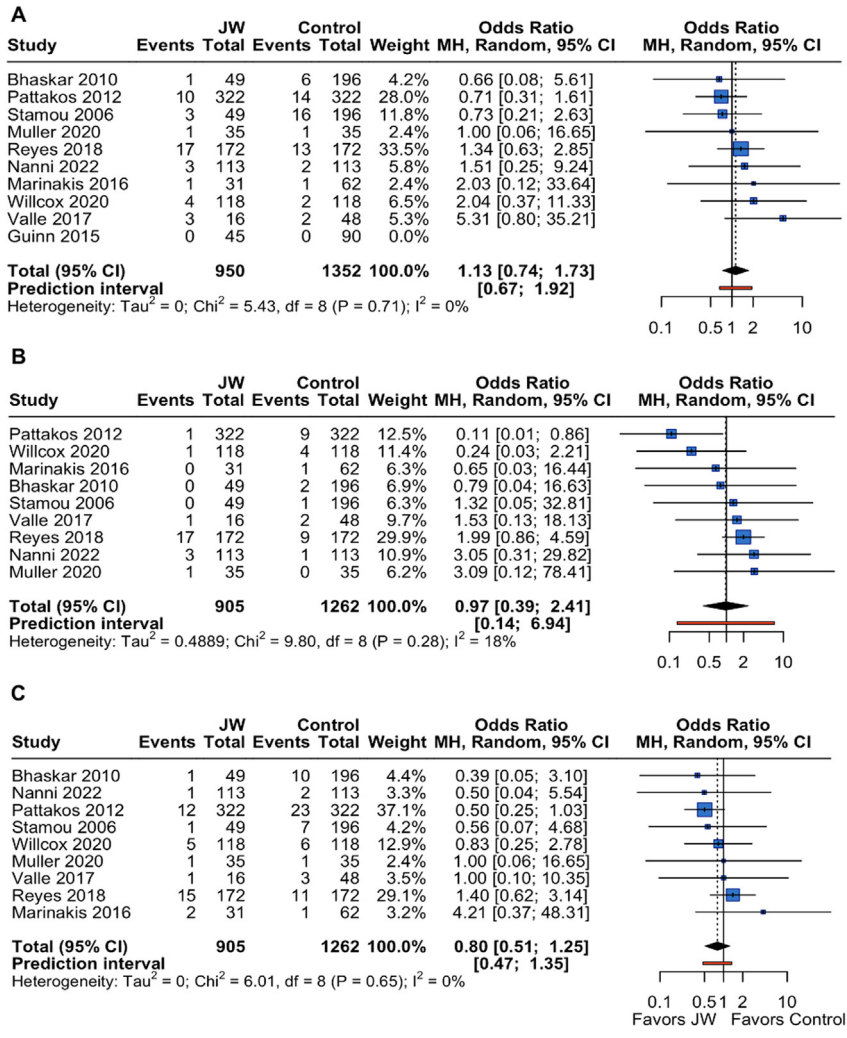

FIG. 2. Forest Plot for binary outcomes of the analysis. Panel A: In-Hospital death. Panel B, myocardial infarction. Panel C: re-exploration for bleeding.Legend CI, confidence interval; JW, Jehovah Witnesses; MH, Mantel-Haenszel.

Discussion

The main findings of the present meta-analysis and systematic review are: (i) JW patients undergoing bloodless cardiac surgery had similar short-term mortality as compared to controls patients; (ii) the occurrence of adverse peri-operative outcomes, such as myocardial infarction and surgical re-exploration for bleeding, were substantially comparable

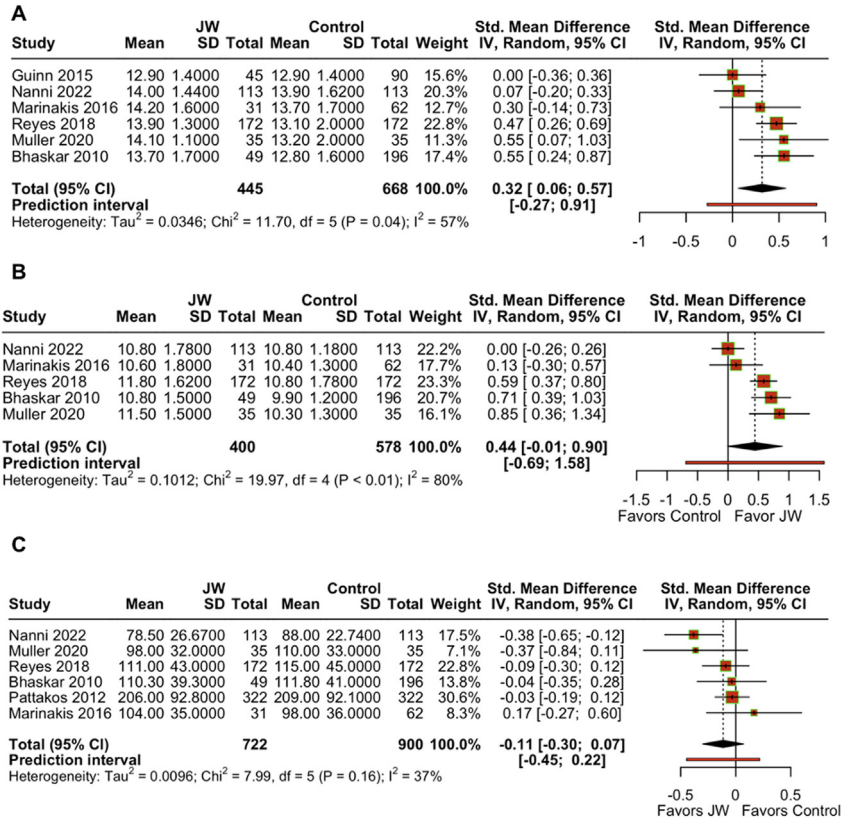

FIG. 3. Comparison of continuous variables. Panel A: preoperative Hb. Panel B: postoperative Hb. Panel C: CPB time. Legend CI, confidence interval; CPB, cardiopulmonary bypass; IV, Inverse variance; Hb, hemoglobin; JW, Jehovah's Witnesses; SD, standard deviation.

between JW patients and controls; (iii) JW patients had higher levels of preoperative Hb with a trend towards higher levels of Hb post cardiac surgery.

As known, Jehovah's Witnesses patients do not consent to receive blood transfusions and the use of blood products based on the Biblical sacred scripture "to abstain from things polluted by idols, from sexual immorality, from what is strangled, and from blood" (Acts 15:20).

Major surgery carries a high risk of bleeding complications, and it has been extensively reported that cardiac surgery is associated with important perioperative blood loss and a high risk of allogeneic blood transfusion.[18]

Given their refusal to accept blood transfusions, major surgery in JW patients is challenging and requires a dedicated and experienced

team.[19,20] In recent years, several studies reported the feasibility of bloodless cardiac surgery with a high potential for a positive impact on patient outcomes.[13,19-21] To the best of our knowledge, this is the largest and most updated meta-analysis of JW patients undergoing cardiac surgery. A previous pooled analysis of the literature by Vasques et al.[4] reporting the results of six studies involving 564 JW patients and 903 controls found that JW patients had higher postoperative levels of Hb, less postoperative blood loss and similar early outcomes compared to controls. While Vasques et al.,[4] provided a pooled analysis of data published up to January 2016, our report includes a meta-analysis based on a larger sample of JW patients, on a total of 10 comparative studies.

Several strategies have been reported to effectively achieve good perioperative outcomes, including the use of erythropoietin or intravenous iron supplementation, intraoperative cell salvage, careful assessment of intraoperative hemostasis, tranexamic agents and optimization of administration of pre and postantithrombotic agents.[22]

Despite some differences in the methods employed for preparing JW patients for cardiac surgery interventions, our study supports the feasibility of transfusion-free approaches in cardiac surgery, in line with the so-called "patient blood management" strategy.[22-24]

Even if bloodless cardiac surgery was traditionally tailored to JW patients, several studies supported a more general implementation of a patient blood management strategy in cardiac surgery[25,26] even outside the specific setting of JW patients. Indeed, there is a consensus that clinically inappropriate use of blood transfusions may be risky and several previous studies reported that red blood cell transfusions may be associated with an increased risk of mortality, acute renal dysfunction, prolonged ventilatory support, cardiac complications, and neurologic events.[27] For these reasons, recent guidelines by the European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anesthesiology emphasized the use of a tailored approach recommending that blood transfusions should be based on the clinical condition of the patient rather than on a fixed hemoglobin threshold.[22]

According to our meta-analysis, a careful patient blood management and appropriate peri-operative assessment and planning, together with the advance of surgical techniques, may allow to achieve good results with low mortality rates in selected patients who refuse blood transfusions, such as JW patients, with comparable outcomes vs. the other candidates to cardiac surgery.

As defined by the World Health Organization, patient blood management is a "patient-focused, evidence-based and systematic approach for

optimizing the management of patients and transfusion of blood products to ensure high quality and effective patient care". Patient blood management is based on three pillars: (i) optimization of the patient's own blood mass; (ii) minimization of blood loss and (iii) optimization of the patient-specific physiological tolerance of anaemia.[23,28-30]

The Western Australian Patient Blood Management Program, a unique, jurisdiction-wide, large-scale experience including over 600,000 patients admitted to four major adult tertiary-care hospitals between July 2008 and June 2014, found that the programme was associated with improved patient outcomes with a decreased mortality, hospital-acquired infection, myocardial infarction and length of hospital stay, reduced blood product utilization and product-related cost savings.[31]

A recent meta-analysis[23] including more than 230,000 surgical patients, most of them related to orthopedic surgery, evaluated the implementation of a patient blood management programme based on the three pillars. Overall, the study reported that the strategy was associated with a reduction in transfusion rates and better clinical outcomes. Interestingly, the specific sub-analysis on cardiac surgery showed similar results in terms of transfusions, hospital length of stay and complications with a trend towards a reduction in mortality (RR 0.92, 95% CI 0.73-1.16, P=0.47)[23]

Patient blood management in cardiac surgery may be particularly challenging given the unique use of cardiopulmonary bypass and the clinical complexity of patients who are often burdened by several comorbidities and polypharmacy, including oral anticoagulants.[32,33] Only a strict collaboration between the cardiothoracic surgeon, the anesthesiologist and the clinical perfusionist may allow an effective and safe patient blood management approach.[29]

Patient Blood Management is not an alternative to blood transfusions when they are clinically necessary but rather an evidence-based, multidisciplinary and multimodal therapeutic approach to individually manage and preserve the patient's own blood in surgical settings.[22,29] Indeed, it should be stressed that despite major surgery can be safely performed in patients who refuse blood transfusions, in-hospital mortality and adverse peri-operative outcomes are particularly high in those who experience severe blood loss and reach very low levels of postoperative Hb.[13] As highlighted by a recent analysis conducted by our group, JW patients with a very low level of postoperative Hb (i.e. values below 8 g/dl at 72/96 h after surgery) not supported by immediate transfusions were associated with a remarkably high mortality rate (up to 40%).[13]

Our results, despite being primarily focused on JW patients, may be of consideration also for candidates to general surgery, reinforcing the need for the implementation of a patient blood management.[34] Taken together our results support the feasibility and the safety of a bloodless cardiac surgery highlighting at the same time that only a coordinated, planned and patient-tailored approach to the patients will allow favorable outcomes.

Our study has some limitations that should be acknowledged. The main limitation relies on the type of studies included. Despite the quality of the studies included was overall satisfactory, this is a pooled analysis of retrospective data with its intrinsic limitations. In all the studies included, JW patients were matched with similar controls in terms of baseline characteristics, surgical risk and type of procedure but we cannot exclude the presence of residual confounders. In addition, most of the centres included were experienced tertiary centres with dedicated surgical teams, thus limiting the generalizability of the results, especially regarding cardiac surgery in an emergency setting. However, no publication bias emerged from our analysis.

Conclusions

In this systematic review and meta-analysis, we found that JW patients undergoing cardiac surgery and not receiving blood transfusions have similar peri-operative outcomes compared with controls in terms of mortality, myocardial infarction, and re-exploration for bleeding.

Our results support the safety and feasibility of a bloodless cardiac surgery in line with a patient blood management approach.

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.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2023.101789.

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