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TRANSFUSION MEDICINE

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Health-related quality of life after restrictive versus liberal RBC transfusion for cardiac surgery: Sub-study from a randomized clinical trial

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Abstract

Background: Transfusion Requirements in Cardiac Surgery III (TRICS III), a multi-center randomized controlled trial, demonstrated clinical non-inferiority for restrictive versus liberal RBC transfusion for patients undergoing cardiac surgery. However, it is uncertain if transfusion strategy affects long-term health-related quality of life (HRQOL).

Study Design and Methods: In this planned sub-study of Australian patients in TRICS III, we sought to determine the non-inferiority of restrictive versus liberal transfusion strategy on long-term HRQOL and to describe clinical outcomes 24 months postoperatively. The restrictive strategy involved transfusing RBCs when hemoglobin was <7.5 g/dl; the transfusion triggers in the liberal group were: <9.5 g/L intraoperatively, <9.5 g/L in intensive care, or <8.5 g/dl on the ward. HRQOL assessments were performed using the 36-item short form survey version 2 (SF-36v2). Primary outcome was non-inferiority of summary measures of SF-36v2 at 12 months, (non-inferiority margin: −0.25 effect size; restrictive minus liberal scores). Secondary outcomes included non-inferiority of HRQOL at 18 and 24 months.

Results: Six hundred seventeen Australian patients received allocated randomization; HRQOL data were available for 208/311 in restrictive and 217/306 in liberal group. After multiple imputation, non-inferiority of restrictive transfusion at 12 months was not demonstrated for HRQOL, and the estimates were directionally in favor of liberal transfusion. Non-inferiority also could not be concluded at 18 and 24 months. Sensitivity analyses supported these results. There were no differences in quality-adjusted life years or composite clinical outcomes up to 24 months after surgery.

Discussion: The non-inferiority of a restrictive compared to a liberal transfusion strategy was not established for long-term HRQOL in this dataset.

Abbreviations: FMI, fraction of missing information; HRQOL, health-related quality of life; MCID, minimum clinically important difference; MCS, Mental Component Score, one of two component summary scores of the SF-36v2; PCS, Physical Component Score, one of two component summary scores of the SF-36v2; QALY, quality-adjusted life years; RCT, randomized controlled trial; SD, standard deviation; SF-36v2 (also SF-36v2®), 36-item short form survey version 2; SF-6D, 6 dimensional health state short form.

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KEYWORDS
cardiac surgery, hemoglobin, quality of life, randomized controlled trial, RBCs, transfusion medicine

1 | INTRODUCTION

For the composite outcome of death, myocardial infarction, stroke, and new-onset renal failure with dialysis at 6 months after surgery, a large international randomized controlled trial (RCT; Transfusion Requirements in Cardiac Surgery III, abbreviated as TRICS III) previously reported that a restrictive RBC transfusion strategy was non-inferior compared to a liberal RBC transfusion strategy in patients who are at moderate to high risk of death undergoing cardiac surgery.[1] Investigating longer-term health-related quality of life (HRQOL) data provides an additional patient-centered outcome of importance.

Both anemia and blood transfusion have been associated with reduced HRQOL. In observational studies, anemia has been linked to reduced HRQOL in various patient populations both with[2,3] and without[4–6] explicit cardiac disease, and a small pilot RCT has suggested that a higher transfusion threshold could improve HRQOL in patients with myelodysplasia.[7] On the other hand, an observational study has suggested that RBC transfusion is associated with worse functional performance based on a quality of life instrument after major cardiac surgery.[8] Nevertheless, these associations have not been consistently demonstrated in other observational studies after cardiac[9] or non-cardiac[10] surgery. Furthermore, without randomization, confounding factors are difficult to adjust for.

In critical care settings, large, multi-center RCTs have compared HRQOL amongst patients with different transfusion thresholds. These have failed to demonstrate statistical differences between groups at 3 months[11] or at 12 months,[12] although one of these studies in a cardiac surgical population found reduction in the secondary outcome of mortality alone in the liberal group at 3 months.[11] No RCTs involving cardiac surgical patients has investigated HRQOL outcomes beyond 3 months with regards to a restrictive compared to a liberal transfusion strategy.

The clinical non-inferiority of a restrictive RBC transfusion strategy in a critical care setting has clear implications for resource savings. However, instead of adopting practice change based on resources alone, it would be appropriate to consider the effect of a restrictive transfusion strategy on other outcomes, such as HRQOL, over a longer term and in a population at high risk for RBC transfusions. In a planned sub-study of the Australian cohort from TRICS III, HRQOL was obtained for up to 24 months after incident surgery to examine the long-term impact of restrictive versus liberal transfusion thresholds on HRQOL. The primary objective of this sub-study was to investigate the non-inferiority of a restrictive versus liberal RBC transfusion strategy on HRQOL at 12 months after surgery. Secondly, we aimed to compare HRQOL at 18 and 24 months after index surgery; and to examine clinical outcomes up to 24 months after index surgery amongst patients receiving a restrictive versus liberal RBC transfusion strategy.

2 | MATERIALS AND METHODS

All patients enrolled in the Australian cohort of TRICS III were invited to participate in this sub-study. All patients were recruited between January 20, 2014 to March 20, 2017. The study was completed March 20, 2019. Ethical review and informed patient consent was obtained (Melbourne Health Human Research Ethics Committee reference number HREC/13/MH/392). Details of TRICS III methodology have been published previously.[1] In brief, inclusion criteria were: 18 years of age or older; scheduled for cardiopulmonary bypass; and a preoperative additive EuroSCORE I[13] of 6 or more. Exclusion criteria were: unable to receive or refusal to receive blood products; involvement in a preoperative autologous donation program; undergoing heart transplantation; undergoing surgery solely for the insertion of a ventricular assist device; and pregnancy or lactation. Eligible patients were randomly assigned in a 1:1 ratio to one of two open-label transfusion strategies (liberal or restrictive) from the start of their surgery to discharge or 28 days postoperatively, whichever occurred first. A centralized, concealed, web-based software using computer-generated random permuted blocks of between two and six was used for randomization, which was stratified according to center. The liberal transfusion strategy had a hemoglobin transfusion threshold of <9.5 g/dl intraoperatively and in the intensive care unit (ICU) while the threshold was <8.5 g/dl on the ward; the restrictive transfusion strategy had a hemoglobin transfusion threshold of <7.5 g/dl throughout the study period.

The 36-item short form survey version 2[14] (SF-36v2) was used to measure HRQOL via telephone at 6 monthly intervals from 12 months after index surgery until

conclusion of the study period, with a minimum commitment of 24 months. The SF-36v2 is the second version of the 36-item short form questionnaire which consists of eight functional domains that contribute to two summary scores: the Physical Component Scores (PCS) and Mental Component Scores (MCS). The eight functional domains of SF-36v2 are: General health, Physical Functioning, Bodily Pain, Vitality, Role-Physical, Social Functioning, Role-Emotional, and Mental Health.

Our primary analysis was based on non-inferiority comparisons of the PCS and MCS at 12 months, after transformation of the scores using population norms developed within Australia.[15] The final transformed score is scaled from 0 to 100, with higher PCS and MCS values indicating better health. A score of zero was assigned to patients who had died. For the Australian population, a mean (standard deviation [SD]) of 50.27 (9.70) for PCS and 52.92 (10.17) for MCS have been reported.[15]

Our major secondary endpoints were the same as the primary endpoint, compared at 18 and 24 months. Additionally, all MCS and PCS values at 12, 18 and 24 months underwent an alternative scoring method on secondary analysis, utilizing licensed software (PRO CoRE 1.5 software, Optum®, Johnston, RI). This scoring method produces a mean (SD) of 50 (10) for both PCS and MCS. This approach has been recommended for research involving SF36v2 to enable international comparisons.[16]

Other secondary endpoint were: Quality Adjusted Life Years (QALY); as well as the original and expanded pooled composite clinical outcomes defined in TRICS III[1] assessed at 12, 18, and 24 months, between randomly assigned groups. QALY was measured by first converting SF-36v2 into a health state measure representing a unitless value between 0 and 1; with 0 representing death and 1 being perfect health. This conversion has been termed the SF-6D (6 dimensional health state short form) and was first described by Brazier et al.[17] for the original SF-36 (version 1). An analogous conversion based on SF-36v2 and the Australian population[18] was used in this study to obtain SF-6D at 12, 18 and 24 months after index surgery. Baseline SF-6D values were taken from population means for age and sex for both randomly assigned groups over time.[18] QALY was measured as the area below the change in SF-6D over time, assuming a linear change between time points. The original pooled composite clinical outcomes in TRICS III were any of the following: death, myocardial infarction, stroke or new-onset renal failure with dialysis. The expanded pooled composite clinical outcome in TRICS III were any of the following: all components of the primary outcome, emergency department visits, hospital readmissions or coronary revascularization.

For the primary outcome and major secondary outcomes, non-inferiority was defined as a one-tailed margin of less than minus 0.25 Cohen's effect size for HRQOL (restrictive minus liberal), meaning that there could be no more than a 2.5 point reduction in PCS and MCS for restrictive relative to liberal group scores. This was chosen as the minimal clinically important difference (MCID) for HRQOL. Two hundred seventy-five patients in each group would allow 90% power to detect a one-sided 95% confidence interval (CI) that was above this non-inferiority limit.[19]

For the secondary outcome comparing pooled composite outcomes, survival analysis was performed using interval censoring with estimated survival curves obtained using the method of Turnbull.[20] The two treatment groups were compared using the log-rank test for interval-censored data.[21]

Our a priori plan for missing data was to impute values using multiple imputation. As multiple imputation relies on assuming that missing values are missing at random, sensitivity analyses was performed under three alternate assumptions: one for data missing completely at random (tested using complete case analysis) and two for data missing not at random (tested by assigning all missing values to worse possible outcome, i.e., death; and by assigning missing values to 50% of imputed value, i.e., assuming a detrimental impact for missing values imputed). As there was no statistical penalty for the description of both one-sided 95% CIs and two-sided 90% CIs using the same data, this was reported as part of the sensitivity analysis.

Statistical analyses were carried out using Minitab 19.2020.1[22] (Minitab, Inc., State College, PA) and R 4.1.0[23] (R Foundation for Statistical Computing, Vienna, Austria) with the mice package[24] (3.13.0; https://amices.org/mice/) for imputation of missing data using the chained equations algorithm.

3 | RESULTS

A total of 12 university-affiliated cardiac centers participated. Of 1546 eligible patients in the Australian arm of the TRICS III study, 629 patients were randomly assigned of which 617 received their allocated randomization (Figure 1). The characteristics of patients randomly assigned to either a liberal (n = 306) or restrictive (n = 311) transfusion strategy are presented in Table 1. As expected from the study design, significant differences were seen in the number of RBCs transfused between groups (liberal 69.9% vs. restrictive 50.2%, OR 0.43 [0.31–0.60]) without significant differences in other blood products (plasma, platelet and cryoprecipitate) or prothrombin complex concentrate usage. Other characteristics were well balanced due to randomization.

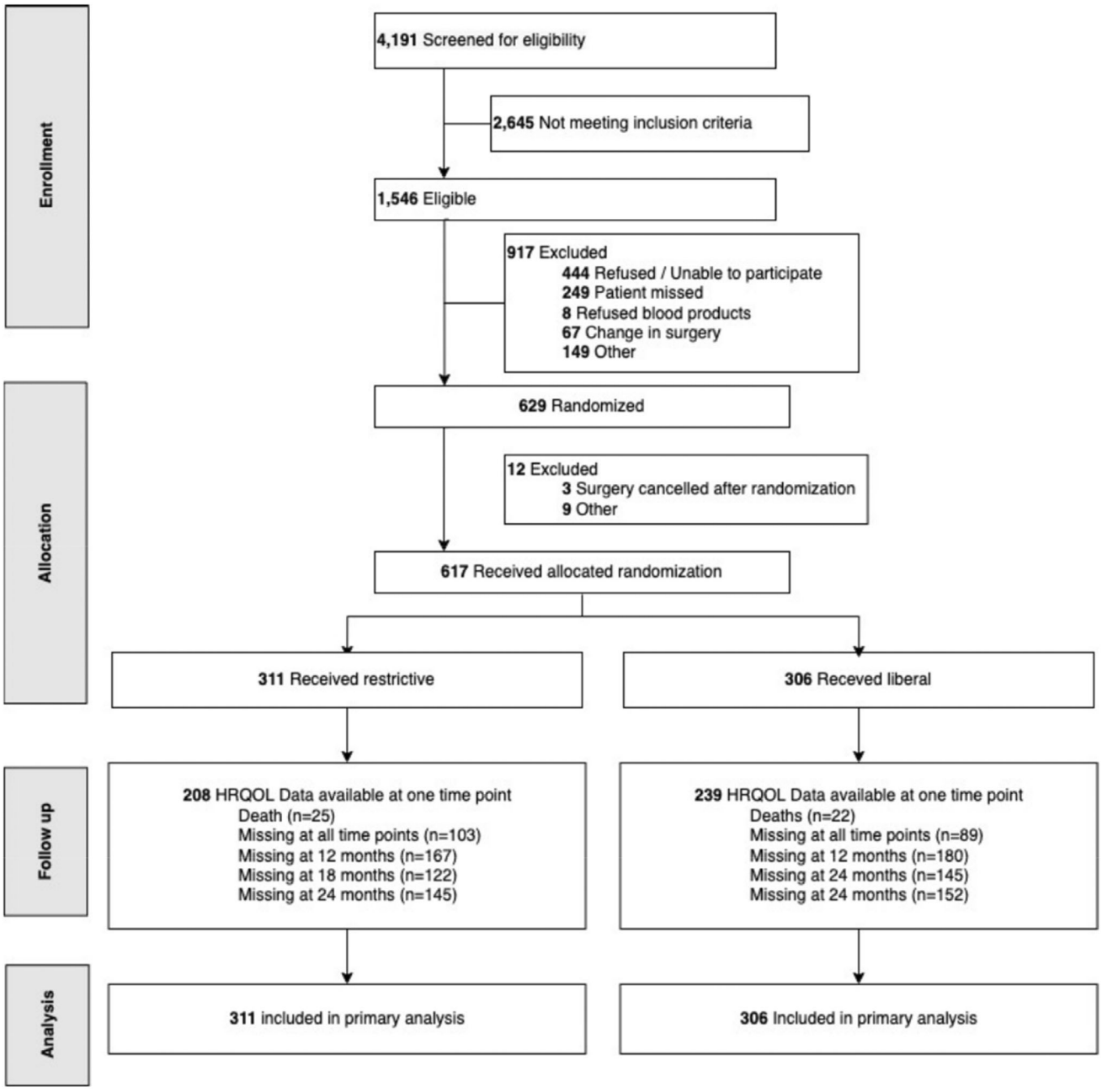

FIGURE 1 Flow diagram of patients analyzed. HRQOL data available (assumed to be zero for death) in 208/311 patients randomly assigned to receive a restrictive RBC transfusion and in 217/306 patients randomly assigned to receive a liberal RBC transfusion. HRQOL, health-related quality of life

Death occurred in 25/311 (8%) in the restrictive group and 22/306 (7%) in the liberal group over 24 months. Data were missing at all time points for 103/311 (33%) in the restrictive group and 89/306 (29%) in the liberal group. HRQOL data were available for at least one time point in 208/311 (67%) in the restrictive group and 217/306 (71%) in the liberal group. Multiple imputation was used to allow for analysis of all 617 patients, on the assumption that data were missing at random (Figure 1). The number of imputations performed was 100 and the variables used in the multiple imputation model are described in the Online Supplementary Data.

3.1 | Primary outcome

The differences in the MCS and PCS (restrictive group scores minus liberal group scores), normalized to Australian values after multiple imputation at 12 months are presented in Table 2 and Figure 2. The point estimate

TABLE 1 Characteristics of patients

Variable	Liberal ($N = 306$)	Restrictive ($N = 311$)	Odds ratio (95% CI)
Baseline characteristics			
Age (years)	73 ± 10	72 ± 11	NA
Male sex	199 (65.0)	212 (68.2)	NA
Body-mass index (kg/m^2)	28.6 ± 5.5	29.2 ± 5.5	NA
EuroSCORE I[13]	8.1 ± 2.0	8.3 ± 2.2	NA
Previous cardiac surgery	41 (13.4)	55 (17.7)	NA
Myocardial infarction within 30 days	12 (3.9)	12 (3.9)	NA
Diabetes	95 (31.0)	95 (30.5)	NA
Treated hypertension	247 (80.7)	248 (79.7)	NA
Emergency surgery	5 (1.6)	2 (0.6)	NA
CABG surgery only	81 (26.5)	88 (28.3)	NA
CABG and valve surgery	72 (23.5)	64 (20.6)	NA
CABG and other, non-valve surgery	34 (11.1)	30 (9.6)	NA
Valve surgery only	75 (24.5)	70 (22.5)	NA
Other, non-CABG surgery	119 (38.9)	129 (41.5)	NA
Duration of CPB (min)	125 ± 63	131 ± 70	NA
Intraoperative tranexamic acid	265 (86.6)	265 (85.2)	NA
In-hospital transfusion outcomes			
RBC transfused	214 (69.9)	156 (50.2)	0.43 (0.31–0.6)
Plasma transfused	76 (24.8)	68 (21.9)	0.85 (0.58–1.23)
Platelet transfused	88 (28.8)	95 (30.5)	1.09 (0.77–1.54)
Cryoprecipitate transfused	47 (15.4)	45 (14.5)	0.93 (0.6–1.45)
PCC transfused	16 (5.2)	17 (5.5)	1.05 (0.52–2.11)

Note: Baseline characteristics amongst patients randomly assigned to receive a restrictive versus liberal red blood cell transfusion strategy amongst Australian patients in TRICS III. All values are expressed as mean ± standard deviation unless otherwise specified.
Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; PCC, prothrombin complex concentrate; TRICS III, transfusion requirements in cardiac surgery III.

for mean difference was −2.6 for MCS and −2.0 for PCS. The lower limit of a one-sided 95% confidence limit breached the non-inferiority limit (−2.5) for both MCS (−5.5) and PCS (−4.4) at 12 months, in favor of a liberal transfusion strategy.

3.2 | Secondary outcomes

After multiple imputation, the differences in HRQOL (restrictive minus liberal MCS and PCS scores) using populations norms for Australia at 18 and 24 months also breached the non-inferiority limit at the lower limit of a one-sided 95% CI (Table 2, Figure 2). Using US instead of Australian population norms to calculate HRQOL scores provided a similar range of differences at 12, 18 and 24 months (Table 2, Figure 2), with the lower limit of one-sided 95% CIs breaching the non-inferiority limit across all time points, again favoring a liberal transfusion strategy.

After conversion of individual SF-36v2 data into SF-6D data (expressed as a value between zero and one), the differences in QALYs (restrictive group minus liberal group) over 24 months between transfusion groups was −0.038 (95% CI −0.103 to 0.028) and did not reach statistical significance ($p = .268$; Figure 3).

On survival analysis, there were no significant differences observed across time between liberal and restrictive groups with regards to either the original pooled composite outcome (death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis) or expanded pooled composite outcomes (all components of the primary outcome as well as any emergency department visit, hospital readmission, or coronary revascularization) (Figure 4). Log-rank tests for interval-censored data failed to show significant differences between groups in the original pooled composite outcome ($p = .733$) or the expanded pooled composite outcome ($p = .772$).

TABLE 2 Difference in HRQOL normalized to Australian and US values after multiple imputation

	Estimated difference in mean MCS: restrictive–liberal (one-sided 95% CI)	Estimated difference in mean PCS: restrictive–liberal (one-sided 95% CI)
Australia		
Time		
12 months	−2.6 (−5.5, ∞)	−2.0 (−4.4, ∞)
18 months	−1.7 (−4.6, ∞)	−0.9 (−3.5, ∞)
24 months	−0.9 (−3.8, ∞)	−1.31 (−3.9, ∞)
US		
Time		
12 months	−2.6 (−5.1, ∞)	−1.8 (−4.2, ∞)
18 months	−2.0 (−4.6, ∞)	−1.1 (−3.6, ∞)
24 months	−0.9 (−3.7, ∞)	−1.5 (−4.0, ∞)

Note: HRQOL was measured using the SF-36v2. The estimated difference in the two summary scores of SF-36v2 (the MCS and PCS) between randomly assigned groups have been derived using Australian and US (United States) population norms, and tabled after multiple imputation. They are mathematically expressed as restrictive minus liberal values with a one-sided 95% CI (confidence interval) provided. FMI for MCS at 12, 18, and 24 months for Australian norms was 0.38, 0.30, 0.23, respectively; and for US norms was 0.30, 0.23, 0.23 respectively. FMI for PCS at 12, 18, and 24 months for Australian norms was 0.30, 0.27, 0.25 respectively; and for US norms was 0.31, 0.26, 0.26 respectively.
Abbreviations: FMI, fraction of missing information; HRQOL, health-related quality of life; MCS, Mental Component Score; PCS, Physical Component Score; SF36v2, 36-item Short Form survey version 2.

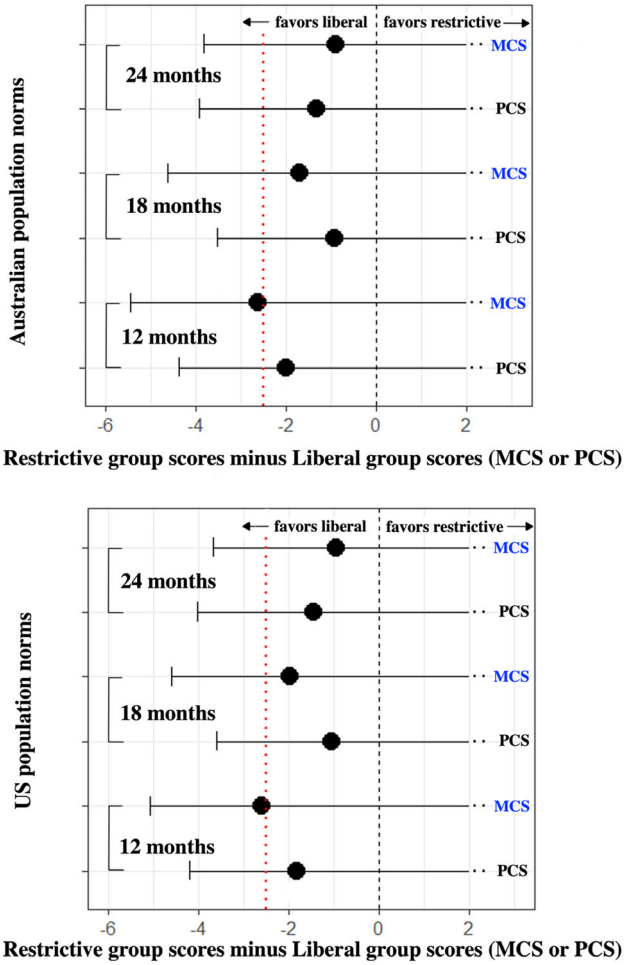

FIGURE 2 Difference in mean scores for MCS and PCS (restrictive group minus liberal group) using Australian and US population norms after multiple imputation. The estimated difference with one-sided 95% CI between the mean scores for MCS and PCS between randomly assigned groups are visually displayed. Changes over time are represented on the *y*-axis. Differences are calculated as restrictive group scores minus liberal group scores, after multiple imputation for missing values. MCS and PCS values are summary scores of HRQOL obtained by the SF36v2, which require scaling based on population norms to provide a value between 0–100. In Australia, a mean (SD) value of 50.27 (9.70) for PCS and 52.92 (10.17) for MCS has been reported, whereas a mean (SD) of 50 (10) is used for both PCS and MCS in US populations. The dotted red line denotes the non-inferiority limit of −2.5. HRQOL, health-related quality of life; MCS, Mental Component Score; PCS, Physical Component Score; SF-36v2, 36-item Short Form survey version 2.

3.3 | Sensitivity analysis

Sensitivity analyses are presented in Tables S1–S3 and Figures S1–S3. These sensitivity analyses reveal the impact of pre-defined assumptions on the widening of the one-sided confidence 95% intervals with a more negative value for the lower limit of this CI and a more negative value in the point estimate for differences between groups. The upper limit of two-sided 90% CIs were below zero (which suggests statistical inferiority) for MCS in 5/6 assumptions at 12 months, 4/6 assumptions at 18 months and 0/6 assumptions at 24 months. For PCS, the upper limit of two-sided 90% CIs were below zero for 2/6 assumptions at 12 months, 3/6 assumptions at 18 months, and 0/6 assumptions at 24 months.

Subsequent post-hoc analysis was performed reporting one-sided 97.5% CIs and its statistically equivalent two-sided 95% CIs for comparison with the initial planned sensitivity analysis (Tables S1–S3). This analysis demonstrates further values that could be contained within a wider CI, with the upper limit of 95% confidence levels below zero for a smaller number of assumptions for MCS values at 12 and 18 months; but not MCS values at 24 months or PCS values at any time.

4 | DISCUSSION

In this study, non-inferiority could not be demonstrated between HRQOL as measured by the summary scores of

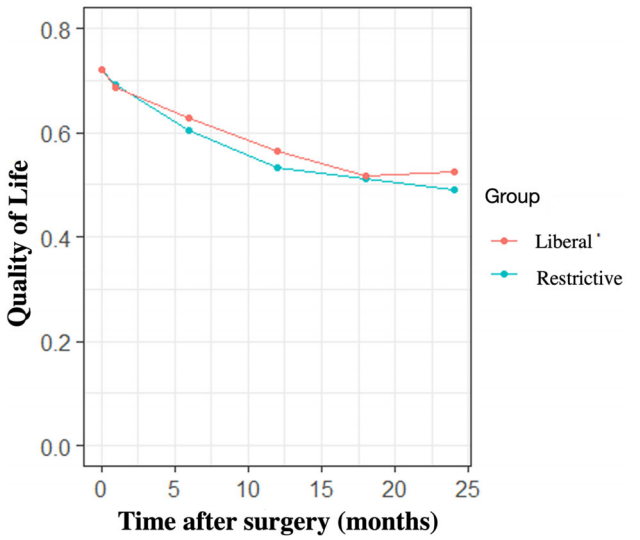

FIGURE 3 QALYs amongst restrictive versus liberal RBC transfusion groups over time. Quality of life is represented as a unitless value between 0 and 1 and derived after conversion of 36-item short form survey version 2 (SF-36v2) data (see text for details). The area under the curve of quality of life over time represents quality-adjusted life years (QALY). Over the 24 month study period, the difference in QALYs (restrictive group minus liberal group) was −0.038 (95% CI −0.103 to 0.028), $p = .268$.

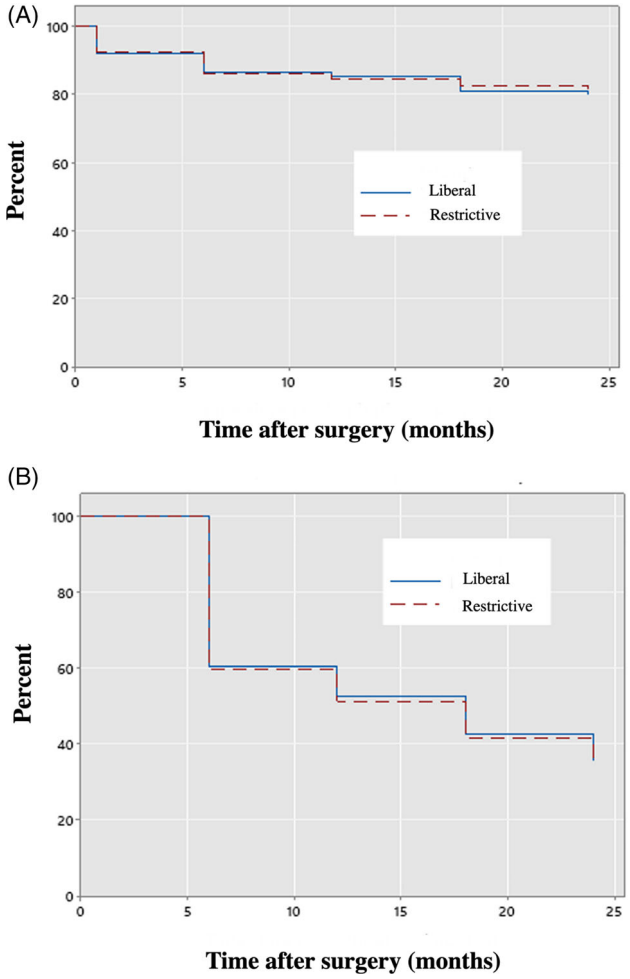

FIGURE 4 Pooled composite outcomes: Restrictive versus liberal transfusion groups over time. Estimated outcome-free survival (in percentage) for (A) original pooled composite outcome and (B) expanded pooled composite outcome between liberal (continuous line) and restrictive (broken line) transfusion groups over time. There was no statistical difference using log-rank test between groups for the original pooled composite outcome ($p = .733$); or for the expanded pooled composite outcome using log-rank test ($p = .772$). [Color figure can be viewed at wileyonlinelibrary.com]

SF-36v2 between restrictive versus liberal transfusion strategies 12 months after surgery. Secondary analysis could not conclude non-inferiority at 18 or 24 months. Sensitivity analysis demonstrated the possibility of statistical inferiority of a restrictive strategy with 90% confidence given certain assumptions, particularly for MCS at 12 months, beyond a threshold regarded as the MCID in a cardiac surgical population with at least a moderate risk of death. As these data are only derived from sensitivity testing, it should only be regarded as hypothesis-generating. Future studies are required to explore the relationship of transfusion strategy on long-term HRQOL in greater detail.

The relationship between transfusion strategy and long-term HRQOL is expected to reflect the balance between the short and long-term risks associated with RBC transfusion[25,26] against the benefits of avoiding transient lower hemoglobin values during the intervention period. RBC transfusion could be associated with long-term HRQOL through the pro-inflammatory and immunomodulatory effects of stored blood,[27] while anemia has been associated with cognitive decline[28] as well as physical functioning,[29] which could be expected to have longer term sequelae. Our findings support the need to better understand the longer term effects of transfusion strategy on HRQOL in vulnerable populations who may be at risk of cognitive or physical decline. Future studies should track hemoglobin levels more closely after discharge; and explore metrics such as the rate of rise of hemoglobin after blood loss or the time spent below anemia thresholds rather than an absolute hemoglobin value at a single point in time; while concurrently measuring physical and mental ability beyond the short term.

This study was a multi-center RCT which minimizes bias and allows for broad applicability. Confining the study to a particular geographical context is also important in HRQOL research as it allows for effective comparisons without significant population variation. This study is notable as an RCT comparing restrictive versus liberal RBC transfusion on outcomes beyond 6 months in patients undergoing cardiac surgery.

Our study was adequately powered at 90% to detect a one-sided non-inferiority margin (with 95% confidence) of minus 0.25 effect size, with the restrictive transfusion threshold set as the comparator (i.e., restrictive minus liberal transfusion HRQOL values). Of note, if we had reported a one-sided 97.5% confidence limit as our primary outcome (statistically equivalent to a two-sided 95% CI), the lower margin would have breached our defined non-inferiority limit by a greater extent because the wider CI encompasses more possible values. A restrictive strategy was the appropriate one-sided comparator given that it is the strategy that is associated with the benefit of reduced costs and demonstrated clinical non-inferiority. A 0.25 effect size was taken to be the definition of MCID in this study for HRQOL. A small effect size has been described as 0.20 and a moderate effect size has been described as 0.50.[30] While the effect size that may be regarded as MCID for HRQOL may lie closer to 0.50 effect size,[30,31] in selecting margins in non-inferiority trials, care must be taken to avoid deliberately large non-inferiority margins that would favor the conclusion of non-inferiority.[32,33] Therefore, our chosen non-inferiority margin was not increased beyond 0.25 effect size.

We confined our analysis to global summary scores for SF-36v2 rather than the eight individual functional domains within SF-36v2 thereby avoiding statistical disadvantage for multiple comparison. Nevertheless, it remains possible that specific domains could have more weight in transfusion trials and warrant further investigation.

This longitudinal study was encumbered by loss of responders over time. This phenomenon is well-described in the elderly population[34] and has been reported in other cardiovascular trials.[2,31,35,36] It is possible that this missing data contain information that is crucial; either because of a substantial difference in quality of life between those who respond compared to those who do not, or because of the influence of other measured variables such as age, sex, co-morbidities, or HRQOL measured at other points in time. However, we minimized the impact of missing data by performing multiple imputation using auxiliary clinical data points and performing sensitivity analysis, which are both recommended strategies.[37] Of note, multiple imputation is still appropriate for reducing bias and improving precision even in the presence of large amount of missing data,[38] particularly in the absence of high fraction of missing information (FMI).[39] The FMI was moderate, lying between 0.23 to 0.30 for most imputed values (Table 2). Our strategy of assigning a PCS and MCS score of zero to patients who died is contentious; and there is ongoing debate about how best to account for death in longitudinal studies measuring HRQOL. Nevertheless, assigning a value of zero for death has not been shown to substantially change the range of possible values derived after multiple imputation, when compared to other strategies used for dealing with death.[40]

29% of patients (444/1546) declined to participate or were unable to participate in our trial and a further 16% (249/1546) were missed. These contributed to the relatively modest 41% (629/1546) of patients actually recruited to the study. While these may have limited how representative our study was compared to the population being investigated (particularly with regards to sicker patients being unable to provide consent or refusal to participate due to culturally and linguistically diverse backgrounds), our recruitment rate was comparable to other pragmatic RCTs in critical care settings that have similar logistical issues to negotiate in implementation.[1,41,42]

One of the possible confounders for HRQOL in our study was hemoglobin at the time of HRQOL assessment.[2,3] However, hemoglobin would be expected to have been similar in both groups by 12 months. No RCTs have been performed focusing on the association of hemoglobin on HRQOL in the cardiac surgical population. Observational studies that have suggested a relationship between hemoglobin and HRQOL cannot exclude the possibility that patient knowledge of increased hemoglobin value influenced their favorable perceptions of health; nor exclude confounders in the relationship such as differences in the management of underlying chronic disease.[2] Additionally, the use of erythropoietin stimulating agents has been shown to improve hemoglobin without concomitant improvements in HRQOL in other settings[43–45] which implies that the relationship between the two is not linear. Furthermore, even though intravenous iron infusion (compared to oral iron or usual care) has been shown in RCTs to be associated with improvements in hemoglobin when given to anemic patients undergoing abdominal surgery,[46–49] improvements in quality of life have not been consistently demonstrated.[47–49]

We did not record baseline HRQOL, which is ideal for calculation of QALY. Nevertheless, it is common in critical care literature for baseline HRQOL to be estimated.[50] Randomization allowed our baseline characteristics to be well-matched, and our assumptions for HRQOL at baseline were taken from appropriate local population estimates. Although a local pre-operative cardiac surgical cohort would have provided more accurate baseline population estimates, we are not aware of any published values from a large sample population. We did not perform a health economic study and therefore incremental cost effectiveness ratios could not be estimated. However, there was only a small difference in QALY between groups, which did not justify a detailed cost analysis.

As with the original TRICS III trial, transfusion strategy was not blinded as it was not feasible. This could have introduced bias in detecting outcomes, however, it

is unlikely that transfusion strategy would be recalled in evaluation of HRQOL 12 months later and beyond. Of note, the trial design of TRICS III did not require assessment of any physiological impact of a low hemoglobin level, as transfusion was based on hemoglobin value alone. However, the absence of requiring physiological triggers could imply a bias toward a non-inferiority which we nevertheless could not establish in our dataset.

In this multi-center RCT, non-inferiority could not be established with a restrictive compared to a liberal transfusion strategy for patients undergoing cardiac surgery at moderate risk of complications with regards to HRQOL at 12 months. Further analysis suggested that non-inferiority could not be established at either 18 or 24 months. This raises the question of possible long-term reduction in HRQOL with restrictive strategies. Future studies are required to explore this relationship further.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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